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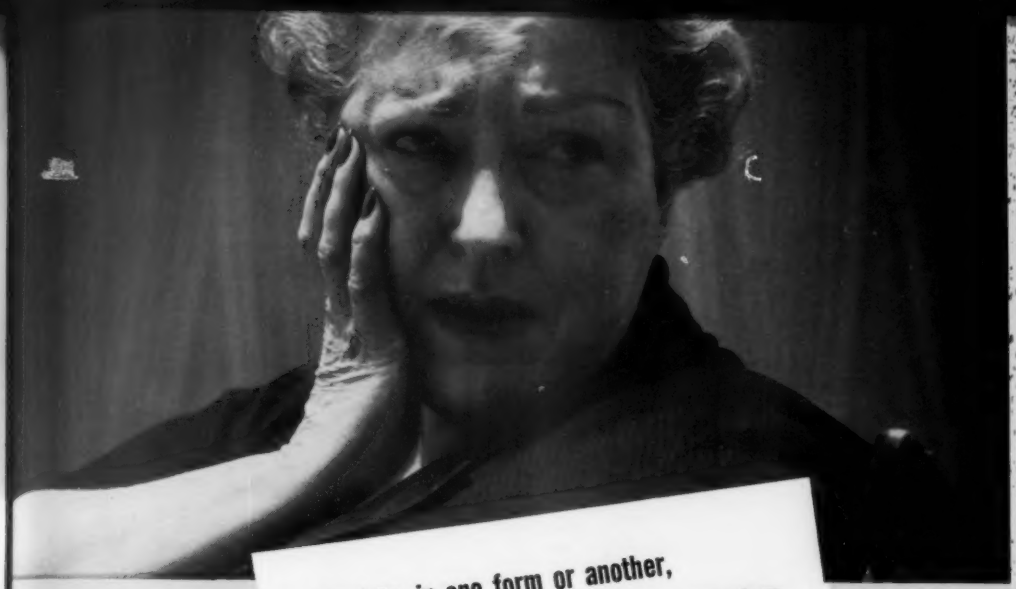

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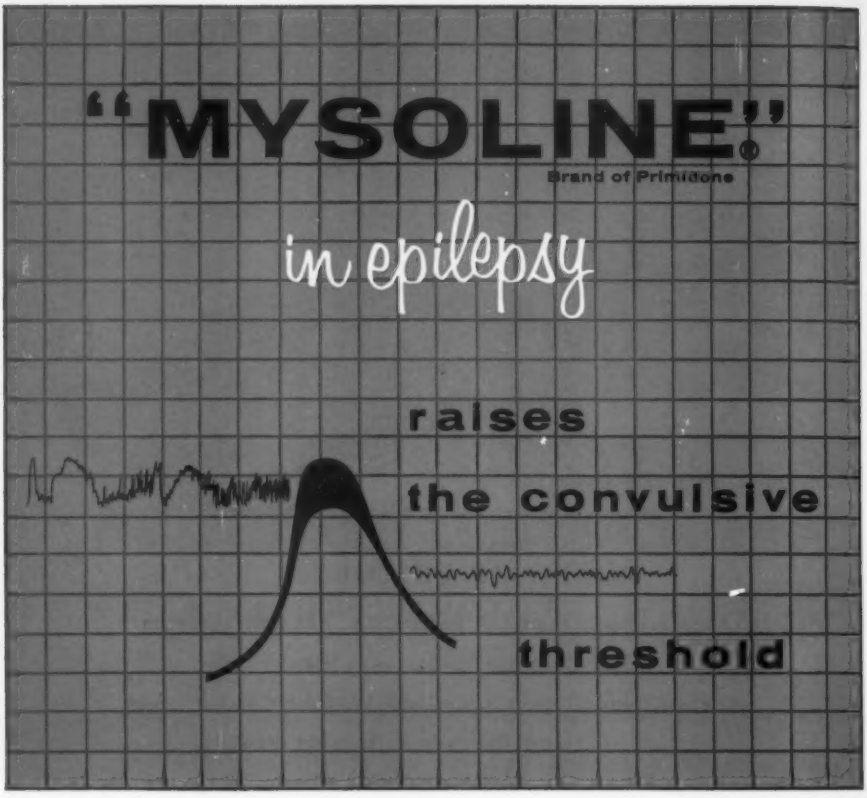

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Neurology Volume 8 • Number 3

Clinical significance of low cerebral spinal fluid pressure

Henry A. Shenkin, M.D. and Bernard E. Finneson, M.D.

THE RECORDING of a low cerebrospinal fluid pressure is still frequently regarded as having little clinical significance. This is true, despite numerous references in the literature to a variety of instances in which decreased intracranial pressure is a characteristic feature. A syndrome of intracranial hypotension following upon cranial operation (as after evacuation of a subdural hematoma), following cranial trauma, or subsequent to a lumbar puncture has been well recognized. A primary syndrome of intracranial hypotension has been less frequently reported,[1,2] and it has been surmised that it results from a decrease in cerebrospinal fluid production for reasons that are not clear at present. It has not been emphasized sufficiently that the cerebrospinal fluid pressure can be influenced by the state of the cerebral circulation and a decreased circulation can reduce the intracranial pressure.

A series of 32 consecutive patients, in whom the cerebrospinal fluid pressure was found to be low on routine diagnostic lumbar puncture, has been collected and is the basis for this report. It emphasizes the importance of this observation as a diagnostic sign and, in particular, illustrates the insight that is afforded into the state of the cerebral circulation in some instances. Patients who had recent intracranial surgery or presented a post-lumbar puncture syndrome, which are well recognized instances of intracranial hypotension, were excluded from this series.

Merritt and Fremont-Smith[3] reported that 94 per cent of 1,033 patients with normal blood pressures and no evidence of intracranial expanding or inflammatory lesions had cerebrospinal fluid pressures ranging between 70 and 180 mm. of water, 5 per cent of the observations were below 70 mm. of water, and the range was from 30 to 220 mm. of water, with the average of 127 mm. Age limits were not given. The possibility is not excluded of some patients having other pathologic processes than those mentioned that could influence cerebrospinal fluid. From our own experience it seems that a cerebrospinal fluid pressure below 70 mm. of water recorded in the lateral recumbent position, with the head held at the same level as the vertebral column and the patient respiring normally, is the lower limit of normality. A reading of 70 to 100 mm. of water pressure is suspiciously low, but not infrequently recordings in this range are obtained in patients who have no apparent clinical or physiologic abnormalities.

The cranial vault and spinal column together with the dura form a semirigid chamber which is completely filled with the brain and spinal cord, the cerebrospinal vascular bed, and the cerebrospinal fluid. Because of the incompressibility of these tissues and the semirigid nature of the walls of this chamber, changes in pressure are chiefly reflected through changes in volume of the contents.

From the neurosurgical services of the Episcopal and Graduate hospitals and the Albert Einstein Medical Center, Philadelphia, Pennsylvania.

Factors causing an increase in these various contents, and consequently an increase in cerebrospinal fluid pressure, are best known and understood. Pathologic processes resulting in a decrease in the volume of these tissues and a consequent fall in pressure are less well understood, but an effort will be made to discuss these possibilities and relate them to the observed clinical states where feasible.

DECREASE IN BRAIN CONTENT

The brain content can be reduced by atrophy, but this is a slow process and undoubtedly is replaced by increase in cerebrospinal fluid spaces without change in total intracranial content. Dehydrated and/or cachectic states will reduce the fluid content of the brain and thereby lead to a decreased intracranial pressure. Undoubtedly cerebrospinal fluid production is also curtailed in this situation and, because of the increased osmolarity of the blood, cerebrospinal fluid absorption is probably increased.

DECREASE IN CEREBROSPINAL FLUID CONTENT

The quantity of cerebrospinal fluid may be reduced by leakage or by a reduction of production. Since no technic has been elaborated to measure production or absorption of cerebrospinal fluid, suggested variations in these functions from normal must remain hypothetical. Thus, in postspinal puncture hypotension that persists for at least some days, it is believed that continued leakage cannot be inferred, at least in sufficient quantity, to explain the maintained intracranial hypotension. Rather, it is possible that a decreased production of cerebrospinal fluid, possibly due to a localized reflex vasospasm of the choroidal vessels and/or disturbance of hypothalamic centers which control spinal fluid production,[4] supervenes upon the original hypotension due to a leakage of fluid and maintains it. A similar mechanism has been suggested for the hypotension noted in the postoperative state[5] and following cranial trauma.[6] However, in these latter instances the mechanism may be somewhat different, since often there is a disturbed state of consciousness, inferring a general decrease in cerebral circulation rather than a localized reflex vasospasm of choroidal vessels alone.[7] Patients with postpuncture hypotension and with primary intracranial hypotension are bright and alert and, therefore, it may be inferred that their general cerebral circulation is within the range of normal. Clinically, all these patients have headache characterized by clear exacerbation in the upright position, or perhaps only present in the upright position.

Fourteen of the 32 patients with decreased intracranial pressure noted in this series were observed after cranial trauma. Ten were found in severely injured persons having cerebral contusions and four after only a cerebral concussion. The lumbar puncture revealing the low cerebrospinal fluid pressure in the severely injured patients was performed generally two to three weeks after injury, and often lumbar puncture shortly after injury had revealed an increased pressure. Persisting headaches, particularly in the upright position, drowsiness, and/or mental obtundity were symptoms which led to lumbar puncture several weeks after the original severe trauma causing the cerebral contusions. Ten patients were observed in this latter category and two illustrative cases are presented.

Case 1. A 42 year old man was admitted to the Albert Einstein Medical Center (Southern Division) on April 5, 1956 after receiving a heavy blow on the head from a falling plank. He was unconscious for an hour and after that he was responsive but somnolent and stuporous. Examination revealed a rigid neck, absent abdominal reflexes, bilateral Babinski, but no focal neurologic signs. He remained disoriented, somnolent, and incontinent for 36 hours. On April 7, 1956 he became more alert but was still disoriented. A long fracture in the left temporal region was seen on a roentgenogram and he had a fracture of the anterior portion of the left first rib. Lumbar puncture revealed xanthochromic fluid under a pressure of 230 mm. of water. By April 9, 1956 he was rational and able to cooperate, but complained bitterly of headache. He improved steadily, but appeared to be rather dull and lethargic and continued to complain of headache. On April 20, 1956 lumbar puncture pressure was 60 mm. of water and the fluid was clear and colorless. He was discharged on April 24, 1956 considerably improved, with only a very mild headache. While under observation his blood pressure ranged from 110/80 to 140/90 and his pulse remained between 82 and 96.

Case 2. A 48 year old man was admitted to the Episcopal Hospital on May 2, 1956 in a semicomatose state, after having been struck by an automobile. There were no focal neurologic signs. The next day he remained disoriented, restless, and

uncooperative and would not take nourishment. He became more talkative and irritable over the next week, and by May 10, 1956 he was clear but still over-talkative, not quite oriented, and his judgment was obviously poor. Nevertheless, he was cooperative. On May 8, 1956 a lumbar puncture was done and the fluid was found to be xanthochromic, with a pressure of 290 mm. of water. On May 18, 1956 he was even more alert and quite cooperative, but he complained of continued, mild headache, worse when he was sitting or standing up. A lumbar puncture was done on this occasion and the pressure was found to be only 60 mm. of water. The fluid was clear. A skull film revealed linear fractures in the temporal and frontal bones on the right side. An electroencephalogram done on May 3, 1956 was diffusely abnormal, but when repeated a month later it was markedly improved and could be considered within normal limits. The patient was last seen two months after his accident and appeared to be completely recovered.

Postconcussion symptoms are frequently difficult to evaluate. However, if the objective evidence of a decreased cerebrospinal fluid pressure is obtained in some cases, it is very helpful in the true assessment of symptoms and indicates a rational therapeutic possibility with a cerebral vasodilator. Four patients who had relatively mild head injuries complained of headache, particularly in the upright position, were found to have decreased cerebrospinal fluid pressures. Two appeared to respond specifically to carbon dioxide inhalations.

Case 3. A 43 year old woman was admitted to the Graduate Hospital on September 22, 1954. The day before admission, when rising from a stooped position, she had struck the vertex of her skull on an overhanging fireplace ledge. She was not immediately unconscious, but about 20 or 30 minutes later she was said to have been unresponsive for three or four minutes. From then until admission she complained of severe headache, particularly when upright, and had occasional blurring of vision. She had been nauseated and vomited once. Neurologic examination on admission to the hospital was entirely normal. Lumbar puncture done on September 23, 1954 showed a spinal fluid pressure of 50 mm. of water. The fluid was clear and colorless and the total protein content was 38 mg. per cent. A skull film was normal. Her blood pressure in the hospital varied from 94/60 to 110/64. She was given 5 per cent carbon dioxide inhalations and within 48 hours she was asymptomatic. She was discharged from the hospital on September 28, 1954 in good condition and, when last seen six weeks after discharge, she had remained free of symptoms.

Spontaneous intracranial hypotension characterized by headache, exaggerated in the upright position, vomiting, rigidity of the neck, and some photophobia has been described previously. Schaltenbrand[1] first hypothesized a decrease in cerebrospinal fluid production as the mechanism of the production of symptoms, but the etiologic factor in these cases remains obscure. We have encountered three patients, all women, that fall into this group. Two had no suggestion of an etiologic factor in the history; the other had chronic, but inactive, bilateral mastoid disease. The use of carbon dioxide inhalations was helpful but did not appear to have permanent effect. In each instance, severe headache detained the patient in the hospital from two to three weeks and persisted in mild form for several weeks thereafter.

Case 4. A 35 year old woman was admitted to the Albert Einstein Medical Center (Southern Division) on June 26, 1955, having complained of severe headache of 24 hours' duration. On admission to the hospital neurologic examination was normal, except for some rigidity of the neck. She had a history of chronic, draining ears but the ears had been dry for the previous few years. Lumbar puncture was done shortly after admission; no pressure could be recorded, since the fluid had to be obtained by aspiration. The fluid was clear and colorless and contained only five cells, all lymphocytes. The blood count was completely normal and the patient was afebrile. A skull film revealed marked sclerosis of the left and mild sclerosis of the right mastoid bone; no actual bone destruction was noted. Roentgenograms of the cranial sinuses were normal. The headache persisted unabated for ten days, markedly increased by the upright position and reduced in intensity in the horizontal position. The blood pressure was always within normal limits, generally 130/90. By July 6, 1955 the headache was somewhat improved and lumbar puncture at this time gave a pressure between 30 and 40 mm. of spinal fluid. At this point fluids were forced and 5 per cent carbon dioxide inhalations for five minutes every hour were begun. This seemed to accelerate improvement and the patient was discharged from the hospital on July 14, 1955. Very mild headache persisted for two more weeks. Since then the patient has remained well.

Case 5. A 24 year old woman was admitted to the Episcopal Hospital on September 7, 1956 with a history of having abruptly developed a severe headache four days previously while ironing clothes. The headache decreased for two days and then became severe again and remained so until admission. The headache was much more severe in the standing or sitting position than when lying down, and the day before admission she vomited three or four times. She also complained that light hurt her eyes. The headache

was generalized but most severe in the frontal regions. Her blood pressure was 100/70, the pulse 72, respirations 28, and temperature 98° orally. There was slight rigidity in the neck but the neurologic examination was entirely normal. A lumbar puncture revealed a zero or negative pressure. The spinal fluid was clear and colorless, with a total protein content of 22 mg. per cent and no cells. Roentgenograms of the skull and chest were both entirely normal. Urinalysis, complete blood count, fasting blood sugar, and blood urea nitrogen were well within the normal range. The patient was markedly improved by 5 per cent carbon dioxide inhalations for five minutes each hour over a period of the next week. However, she still had headache when upright, and on September 16, 1956 the second lumbar puncture revealed the pressure still to be zero and the fluid had to be obtained by aspiration. Nevertheless, she insisted on being discharged from the hospital so she might look after her small children.

She returned to the hospital on October 8, 1956 because the headache had resumed its original intensity, particularly in the upright position. Lumbar puncture again revealed the absence of pressure, yet the cerebrospinal fluid was normal. On October 10, 1956 a bilateral cerebral arteriogram was carried out and proved to be normal in all respects. An electroencephalogram was entirely normal. Carbon dioxide inhalations and the forcing of fluids was resumed, the patient gradually improved, and she was discharged on October 16, 1956. By November 1, 1956 she had completely overcome her headaches and has remained completely well since.

Four patients were seen in consultation because of vertiginous symptoms. In addition, they had complaints not directly attributable to the labyrinthine apparatus, consisting of feelings of a heaviness of the head, perhaps lightheadedness of a constant nature, and occasionally headache. They were found to have intracranial hypotension on lumbar punctures. The patients were elderly, 55 to 68 years of age, and two had hypertension. After observation, it appears logical to believe that their vertiginous symptoms were vascular in origin, perhaps due to focal insufficiency from the basilar artery complex, and that the intracranial hypotension and accompanying symptoms of general cephalic nature were due to reduced cerebrospinal fluid production, either of reflex or direct vasospastic origin. These patients were clear and alert mentally, and it seemed unlikely that they suffered any generalized reduction of cerebral circulation.

Case 6. A 59 year old sthenic man was admitted to the Graduate Hospital on August 18, 1954. He had been well until about six weeks before admission when he began to experience vertigo and a tight feeling about his head. He also complained of "black spots" before his eyes. Since these symptoms continued and he was unable to get out of bed because of the vertigo, he was admitted to the hospital. In addition to vertigo, he stated that he had had some headache in the four to five weeks prior to hospitalization. His blood pressure on admission was 196/102 and roentgenographic examination of his chest revealed slight left ventricular enlargement with some dilatation and elongation of the aorta. There was slight prominence of the vascular markings throughout both lung fields. Neurologic examination was normal, except for unsteadiness of gait and a positive Romberg test. A skull film was normal. Lumbar puncture was done on August 19, 1954 and the initial pressure was 60 mm. of water. There were two lymphocytes in the spinal fluid and the spinal fluid protein content was 47 mg. per cent. Routine blood chemistry examinations and urinalysis were normal. Otologic consultation stated that his hearing was good and responses to caloric stimulation were normal, though diminished in duration and amplitude. He was placed on carbon dioxide inhalations (5 per cent in 95 per cent oxygen for ten minutes every hour) with some improvement and discharged from the hospital on August 23, 1954.

Case 7. A 62 year old woman was admitted to the Graduate Hospital on February 23, 1956 with a four-week history of episodes of vertigo occurring many times daily. On two occasions she had fallen during these attacks. Two weeks before admission she first noticed a heaviness and a ringing in her left ear. She did not complain of headache specifically, but described a "dullness" of her head and nausea which was less noticeable when she was supine. Her blood pressure ranged from 110 to 130 systolic and 64 to 70 diastolic. Neurologic examination was normal, except for a moderately positive Romberg test. Roentgen examination of the skull revealed sclerosis of the left mastoid bone. The electroencephalogram was within the range of normal variability. A lumbar puncture was done on February 27, 1956; the pressure was found to be 40 mm. of spinal fluid and the cerebrospinal fluid protein content was 42 mg. per cent. Otologic consultation reported slight diminution of hearing in the left ear. Caloric responses were normal in the right ear, but there were perverted responses from the left vestibular canals. An opinion was offered that this patient had labyrinthosis. Carbon dioxide inhalations resulted in improvement in the symptoms of heaviness of her head and she was more comfortable when out of bed. Although placed on Dramamine, she still had episodes of vertigo when discharged from the hospital on March 7, 1956.

DECREASE IN THE CEREBROVASCULAR BED

Studies on the effect of change of carbon dioxide content of the blood on the cerebral

circulation reveal most dramatically the influence of the size of the cerebrovascular bed upon the intracranial pressure. Five per cent carbon dioxide inhalation causes a 43 per cent rise in cerebrospinal fluid pressure accompanying the 55 per cent increase in cerebral blood flow.[8] Cobb and Fremont-Smith[9] first noted that hyperventilation decreased the cerebral blood flow and the cerebrospinal fluid pressure. This has been confirmed in our laboratory, using the more precise nitrous oxide technic for measuring cerebral blood flow; a 31 per cent decrease in cerebral blood flow reduced the cerebrospinal fluid pressure 27 per cent.[10] Ryder and co-workers,[11] using drugs whose effects on the cerebral blood flow could be estimated, concluded that changes in cerebral blood flow always induced changes in the cerebrospinal fluid pressure in the same direction.

Studies previously published[12] on the effects of hypertension and arteriosclerosis on the cerebral circulation of man can be correlated with unpublished data on cerebrospinal fluid pressure concomitantly measured to further illustrate this point.

TABLE 1

	CBF	*CSFP*	*MABP*
Normals (mean of 12 patients)	53	202	91
Arteriosclerotics (mean of 11 patients)	51	202	94
Hypertensive arteriosclerotics (mean of 10 patients)	35	180	134

Table 1 reveals that there is a significantly lower cerebrospinal fluid pressure in patients with hypertension and arteriosclerosis who have a decreased cerebral blood flow, as contrasted to normal patients and patients only with arteriosclerosis who have normal cerebral blood flow values. The spinal fluid pressures in these studies were recorded with the patient in the supine position and are somewhat higher than similar pressures measured in the lateral recumbent position.

From the evidence cited above, it may be concluded that in clinical situations where the cerebral circulation is lowered, and presumably there is a reduction in the size of the cerebrovascular bed, it would be reflected in a decrease in the cerebrospinal fluid pressure. It may also be presumed that, if the circulation is reduced, spinal fluid production could be curtailed and this would be a secondary factor in lowering spinal fluid pressure. Indeed, we have encountered 11 patients who were suspected of harboring an intracranial mass lesion because of their mental obtundity. The finding of a decreased cerebrospinal fluid pressure in these patients was often the first indication that the mental obtundity was due to a relatively acute depression (or insufficiency) of the cerebral circulation. In several instances the use of a cerebral circulatory stimulant (carbon dioxide inhalations) and other general measures, such as repair of dehydration, caused remarkable improvement in the status of the patient.

Case 8. A 56 year old man was admitted to a general hospital from a psychiatric institution on October 21, 1954. He had been melancholy for about one year and had been receiving shock therapy over the preceding three weeks. For fiive or six days he had been becoming duller, and on the day previous to admission it was noted that he was very lethargic and somnolent and he had weakness of his left extremities. Because of the somnolence and progressive deterioration, he was transferred to a neurosurgical service with the thought that he might have a brain tumor. Examination revealed a very lethargic individual looking older than his stated age. His blood pressure was 134/80. He was oriented for person but not for time or place. He had a marked left central facial weakness with considerable weakness of his left arm and relatively less weakness of the left lower extremity. No other positive neurologic changes were found. Roentgenograms of the skull and chest were normal. The pineal body could not be visualized. A lumbar puncture demonstrated clear spinal fluid under a pressure of 60 mm. of water. The spinal fluid contained two lymphocytes and 48 mg. per cent of protein. A diagnosis of cerebrovascular insufficiency was made, possibly induced by shock therapy superimposed upon cerebral arteriosclerosis. He was treated with inhalations of carbon dioxide and adequate fluids were administered by mouth. The patient improved promptly, strength returned to his left extremities and face, he became more alert and ambulatory and could be discharged from the hospital on October 26, 1954, six days after admission.

Case 9. A 70 year old woman was admitted to the Episcopal Hospital on December 20, 1954. She had been developing progressive weakness of her left extremities for three or four months. For six weeks she had complained of nausea and three days prior to admission she began to complain of headache. It was also noted that she had some personality changes. On admission her blood pressure was 146/80, she had a definite left facial weakness and some weakness of her left extremi-

ties, and a cogwheel phenomenon was noted when testing the tonus of both upper extremities. Skull films were normal, except for calcification of both internal carotid arteries. The pineal body was not visualized. A lumbar puncture on December 24, 1954 revealed a spinal fluid pressure of 70 mm. and the spinal fluid protein content was 68 mg. per cent. Total serum cholesterol was 465 mg. per cent. A diagnosis of cerebrovascular insufficiency due to cerebral arteriosclerosis was made. Under a regime of general hospital care, including attention to adequate hydration, anticoagulant therapy, and low-fat diet, she improved markedly and was discharged on January 4, 1955.

Case 10. A 65 year old man was admitted to the Episcopal Hospital on April 26, 1956. This man was a known diabetic for four years and had been taking insulin, but in recent months had not been checked by a physician. Five days prior to admission he had fallen down two steps and suffered a small laceration of his scalp in the right frontal region. Two days before admission he had become lethargic, confused, and disoriented. On admission to the hospital he was definitely obtunded and disoriented. His blood pressure was 160/80, pulse 85, and respirations 22. He had clear weakness of his left face and upper extremity. Lumbar puncture revealed clear fluid with a pressure of 44 mm. The spinal fluid protein was 68 mg. per cent and the spinal fluid glucose was 128 mg. per cent. Fasting blood sugar was 390 mg. per cent. A roentgenogram of the skull was normal, with the pineal body in the midline. A diagnosis of uncontrolled diabetes and cerebrovascular insufficiency was made. It seemed unlikely a subdural hematoma had collected. He was hydrated and his diabetes brought under control. He improved slowly, although his diabetes was difficult to control. He was discharged on May 23, 1956, mentally alert and without evidence of any focal muscular weakness.

Case 11. A 66 year old man with a previous history of alcoholism, arteriosclerotic heart disease, and hypertension with occasional episodes of heart failure was admitted to the hospital on May 21, 1956. He had been taking digitalis. On the day of admission he had a "dizzy spell" while getting out of bed and fell to the floor. When he remained stuporous, he was brought to the emergency ward where his blood pressure was found to be 160/90 and he showed no evidence of cardiac failure. He was stuporous and did not respond to questions. He had definite weakness of the right side of his body, with a right Babinski. Lumbar puncture revealed a pressure of 64 mm., the fluid was clear and colorless, and the total protein content was 56 mg. per cent. A skull film was normal and the pineal body was in the midline. The next day his right lower extremity appeared stronger and his blood pressure was 130/80. On May 23, 1956 he was improved; he was more alert and the right hemiparesis had disappeared. On May 24, 1956 he was talking more clearly, was more alert, and was eating. On May 27, 1956 he became confused, irrational, disoriented, and very noisy in the middle of the night and remained so for 24 hours. On May 28, 1956 he was much quieter but he remained irrational from time to time. Neurologic consultation revealed that he was quite stuporous, muttering, and could not cooperate fully in the examination. It was believed that he was definitely aphasic. There was a right central facial weakness, but he moved all four extremities well. It was felt that he had a cerebrosvascular insufficiency syndrome, no intracranial mass lesion was present. On general supportive therapy he gradually improved, the aphasia cleared, he became ambulatory, and was discharged on June 14, 1956.

Of course, shock states from whatever cause would decrease the cerebral circulation, as it does all other parts of circulatory apparatus, and it can be presumed this would be reflected in a decreased cerebrospinal fluid pressure. One patient was encountered in whom the suggestion of a subdural hematoma was raised because of stupor and a recent history of a cranial trauma. While the true diagnosis was not difficult to determine, the low cerebrospinal fluid pressure helped orient the consultant concerning the pathophysiologic mechanisms present.

Case 12. A 48 year old woman was brought to the accident ward of the Albert Einstein Medical Center (Southern Division) by the police with only the history that she had fallen down a flight of stairs about 72 hours previously and that she had become progressively more stuporous over the past 24 hours. She was admitted to the hospital as a subdural hematoma suspect and when seen shortly thereafter her blood pressure was 70/50. Obscured by ecchymosis of her face and about her eyes was a definite jaundice of her sclera. Neurologic examination revealed no diagnostic signs, and clear cerebrospinal fluid under a pressure of 40 mm. was found on lumbar puncture. A diagnosis of hepatic coma and shock was made. Despite supportive therapy, the patient expired ten hours after admission. Postmortem examination confirmed the diagnosis of advanced liver cirrhosis and no intracranial hemorrhage was found.

A particularly interesting experience in which a decreased cerebrospinal fluid pressure gave the first indication of the proper diagnosis was a patient with chronic barbiturate intoxication who was admitted to the hospital as a subdural hematoma suspect. When a low intracranial pressure was noted on routine lumbar puncture, the initial diagnostic impression of a subdural hematoma was super-

seded by the thought she was suffering with a disturbance of consciousness due to toxicity of either endogenous or exogenous origin.

Case 13. A 50 year old woman was involved in an automobile accident two months prior to admission to the Episcopal Hospital on March 22, 1956 as a subdural hematoma suspect. She had suffered a compound skull fracture and facial injuries resulting in blindness of both eyes. One eye had to be removed. She also fractured both humeri and several bones of the forearms. Her brain injury was never too severe, but she was said to have had considerable pain requiring large doses of medication for its relief. An added factor was that the patient was involved in the automobile accident while she was eloping with a man other than her husband and this created a severe emotional disturbance. She had had considerable headache in recent days and had been staggering while walking about her home. She had become progressively more obtunded mentally and on admission she was disoriented and confused. Neurologic examination was essentially normal as far as it could be carried out. Her blood pressure was 128/80 and routine blood determinations were normal. There was no evidence of dehydration. A lumbar puncture was done on March 22, 1956 and the initial pressure was found to be 60 mm. of water, the fluid was clear and colorless, and the spinal fluid protein content was 37 mg. per cent. With the evidence of a low cerebrospinal fluid pressure, it was thought that she probably had an intoxication rather than a subdural hematoma. The additional history was now obtained that she had large amounts of long-acting barbiturates daily up until three days before admission and that these were available to her for self medication. These sedatives were taken in addition to analgesics. There was no abnormal concentration of bromides in her blood. Two days after admission her urine was collected for a qualitative barbiturate determination and, although she had not had any barbiturates in the hospital in the preceding 48 hours, a positive test was obtained. A skull film was normal, but the pineal body was not visualized. An electroencephalogram on her second hospital day was diffusely abnormal, with the suggestion of maximal involvement in the right temporal area. All medication was withheld except for occasional doses of paraldehyde, and by March 29, 1956 she was markedly improved. She was discharged on March 30, 1956 in good condition and in full possession of her senses.

SUMMARY

Representative cases have been presented from a series of 32 consecutive patients in whom a low cerebrospinal fluid pressure had been obtained on routine diagnostic lumbar puncture. The cases fell into the following categories of cerebral hypotension: 1) following cranial trauma, 2) primary (spontaneous), 3) associated with vertigo, and 4) accompanying a decrease in cerebral circulation.

In general, it is believed that a low cerebrospinal fluid pressure is too often disregarded as having clinical significance, and, specifically, its possible relationship to the state of the cerebral circulation is unappreciated.

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Posterior hypothalamic hamartomas and gangliogliomas causing precocious puberty

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PRECOCIOUS PUBERTY is known to occur with neoplasms of the ovary, testes, and adrenal gland or with certain lesions of the pineal and hypothalamic areas of the brain. Among this intracranial group, some congenital tumorous masses arising from the posterior hypothalamus produce the syndrome of precocity so consistently that one may speak here of a definite clinicopathologic entity. The lesions under consideration are the hamartoma (that is, heterotopic hyperplastic malformation) and the closely related dysontogenetic ganglioglioma of the posterior hypothalamus. Two such proved cases are presented in this study and 14 verified cases from the literature are reviewed briefly.

The first patient was followed from the age of two years until her death at the age of 15 years and nine months; complete autopsy was obtained. The second patient was first seen at the age of two and one-half years and is still living (now three years and nine months old); his lesion was verified by surgical biopsy.

CASE REPORTS

Case 1. A girl was born on January 16, 1939, the third child of healthy parents, without familial background of neurologic disorder. The child was normal at delivery but developed seizures a few months after birth. The brief attacks, occurring as often as 20 to 30 times a day, consisted of momentary staring, blinking of eyes, and quick twitching of arms, without loss of consciousness. At the age of two years and eleven months (December 1941) she was examined for the first time at the University of Michigan Hospital. She appeared to be physically overdeveloped and looked like a five year old child. Her height was 101 cm., her weight 17.9 kg. Signs of precocious puberty were noted, such as pubic hair, enlarged clitoris, and prominent breast development. Her bone age was four to five years. General physical, neurologic, and laboratory studies were all negative. When reexamined at the age of three years and three months (April 1942) her height was 106.3 cm., weight 21.15 kg. The genital development was that of a 12 year old girl, but her mental state corresponded to her age. There were no psychosexual deviations. Blood pressure was 135/80. Urinary estrogens were 2 RAT units, pituitary follicle stimulating hormone was negative, and the 17-ketosteroids were 22(?) mg. in a 24-hour urine specimen.

On her third hospital admission (February 1943) she was first seen by one of the authors at the age of four years, one month. She looked like a girl of seven (figure 1A); her height was 115 cm., weight 23.85 kg. (figure 2). The signs of precocious puberty had increased further. Her behavior was fickle, with a tendency to violent emotional outbursts. Her mental performance (as determined by psychometric tests) was that of a five year old child. Frequent petit mal-like attacks were observed which were initiated either by an episode of laughing or crying. Neurologic examination was again normal.

The electroencephalogram showed low-voltage, fast background activity, with seven to eight per second waves and very few 8.5 to 9 per second alpha waves. Occasionally, medium to high-voltage (200 mv.) 3 to 5 per second waves with or without positivity occurred in all anterior leads, especially on the left, but no true spike-wave pattern was seen. Roentgenograms of the skull revealed erosion of posterior clinoid processes. The cerebrospinal fluid was normal. Pneumoencephalography disclosed a walnut-sized mass in the posterior hypothalamic region encroaching upon the third ventricle and midbrain (figure 3A). The lateral ventricles were slightly dilated.

On the basis of these findings the diagnosis of hypothalamic tumor associated with precocious puberty and convulsive and behavior disorders was made. In October 1946, at an age of seven years and nine months, the patient was seen again. She measured then 146.3 cm. in height and weighed 58.5 kg. (fig. 2). The development of breasts, pubic hair, and external genitalia was that of an adolescent girl. The seizures had continued uncontrolled, starting usually with laughter or grimacing, then stiffening out, and falling without losing consciousness. When twitching of the limbs

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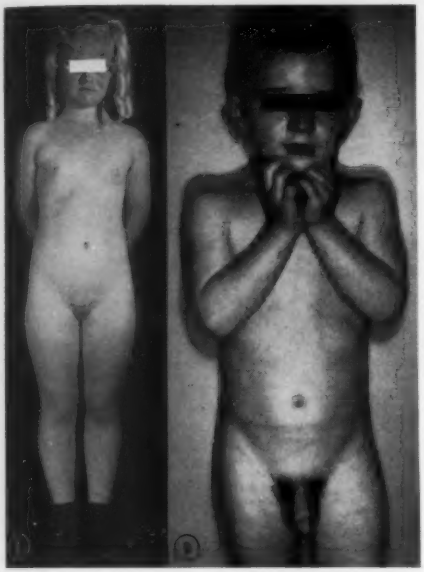

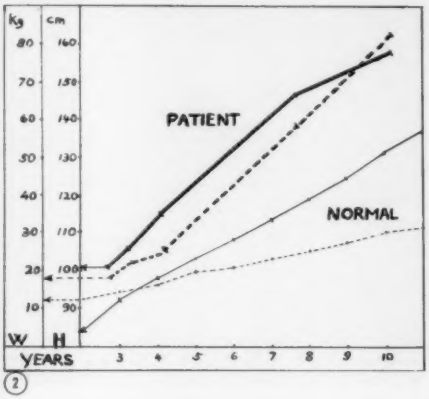

FIG. 1. *A*, photograph of *case 1* at age four years. *B*, photograph of *case 2* at age three years.

FIG. 2. *Case 1.* Curve of patient's weight (W) and height (H) compared with that of a normal child, plotted against age.

occurred it was more marked on the right side. Mental performance had fallen below her age; she was restless, distractible, and mischievous. Neurologic examination was negative except for horizontal nystagmus.

At the age of ten years and two months (March 1949) the patient had further deteriorated mentally, while the attacks and excessive physical growth continued. She had now become very obese and reached the extreme weight of 83.25 kg.; her height was 157.5 cm. She had purple striae and fully developed external genitalia and secondary sexual characteristics, yet had not menstruated. Her behavior was silly and expansive, with uninhibited emotional outbursts.

She was subsequently hospitalized at the Caro (Michigan) State Hospital for Epileptics (January 1949 to December 1951) where additional observations were made. Menses started at 11 years of age. Basal metabolic rate was minus 28. Many seizures were observed which invariably began with uncontrollable laughter or crying. In the more severe attacks her pupils dilated.

Repeated electroencephalograms (figure 4) showed abnormal paroxysmal records with left-sided predominance; they were considered characteristic for a convulsive disorder originating from a deep level. Bursts of 100 to 150 mv. abortive or genuine three per second spike-waves or sharp spikes occurred episodically over both hemispheres, with slight emphasis on the left frontal and right temporal regions, though sometimes more spikes were seen over the left temporal region. The paroxysmal bursts occurred for about 60 to 70 per cent of the time of the recording (40 minutes). Swallowing and oral movements were observed during some of the spike-wave discharges. Initially, there were normal 9 or 10 per second alpha waves in the occipital leads. During a clinical attack, more medium and high voltage 6 to 7 per second waves were seen over the left than over the right hemisphere, while the latter showed more 9 to 10 per second alpha and low-voltage fast activity, with superimposed muscle artefacts. During the continued attack of laughter, muscle artefacts obliterated the genuine waves; 20 seconds after the attack the 4 to 5 per second waves again prevailed on the left, whereas on the right the 9 to 10 per second alpha and fast low-voltage activity was more prominent.

At the chronologic age of 11 years and four months, her mental age was five years and nine months; her I.Q. was 51, according to the revised Stanford-Binet scale. Bender Visual-Motor-Gestalt test showed a maturational level of five to six years, indicative of brain damage and little emotional control.

After discharge home, she became progressively obese and had attacks of unexplained high fever. She was admitted to Butterworth Hospital, Grand Rapids, Michigan, on September 27, 1955, comatose and in status epilepticus. Her temperature ranged between 40.5 and 41.7° C.; there was evidence of pneumonia and lower nephron syndrome with anuria. She died at the age of 15 years and nine months (October 5, 1955).

At autopsy there was extreme obesity, pneumonia of the left lower lobe, tubular nephrosis, and

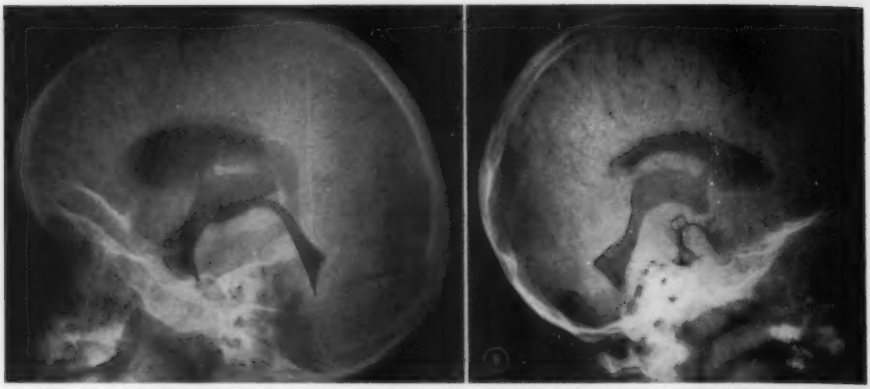

FIG. 3. *A*, lateral pneumoencephalogram, *case 1*, showing large mass in the interpeduncular space displacing third ventricle and aqueduct. *B*, pneumoencephalogram, *case 2*, showing small mass in the interpeduncular space. Illustrations have been retouched.

acute hemorrhagic erosions of the esophageal, gastric, and duodenal mucosa. The adrenals, ovaries, and the pituitary gland were normal macroscopically and microscopically.

At the base of the brain there was a nodular mass about the size of a golf ball which had a firm rubbery consistency and the same color as the brain (figure 5A). Although in a midline position, it spread slightly more to the left. It extended rostrally to the optic chiasm and infundibulum and completely covered the mammillary bodies, the posterior perforated space, and the cerebral peduncles. The caudal pole of the mass concealed the ventral surface of the pons and reached the brachia pontis. The second to sixth cranial nerves and the basilar artery were seen to tunnel freely through the mass. On coronal sections the growth was attached only to the region of the left mammillary body by a broad pedicle; otherwise, the lesion was completely free and separated from the brain by a normal subarachnoid space (figure 5B). Rostrally the lesion extended to the level of the anterior commissure, surrounding and elevating the optic tracts and displacing

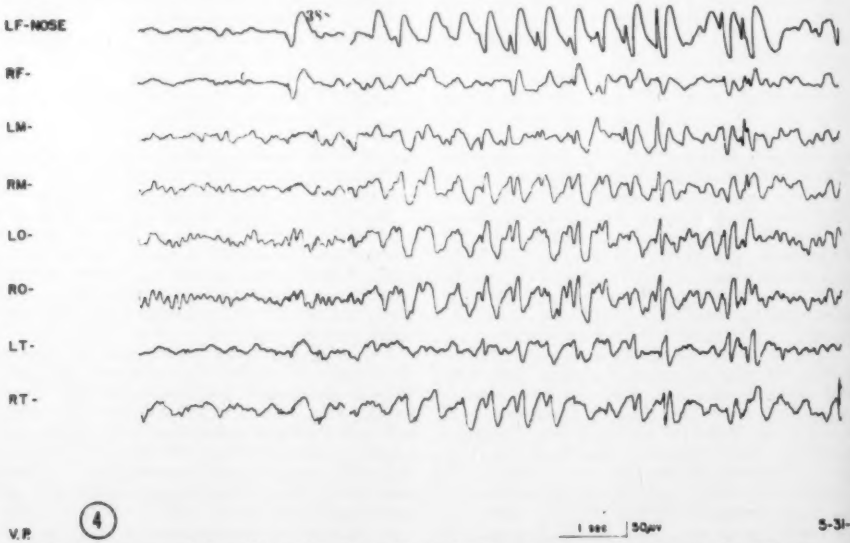

FIG. 4. Electroencephalographic tracing of *case 1*, showing deep level convulsive discharges in all leads.

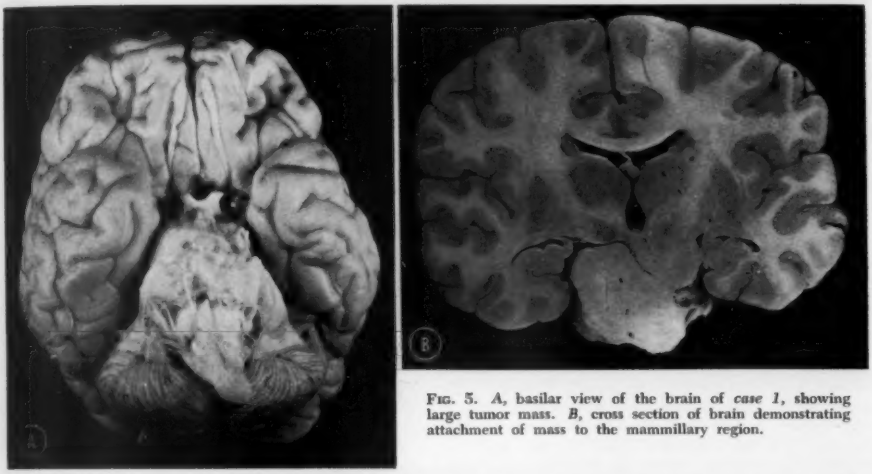

FIG. 5. *A*, basilar view of the brain of *case 1*, showing large tumor mass. *B*, cross section of brain demonstrating attachment of mass to the mammillary region.

the hippocampi laterally. The ventral surface of the pons was markedly indented, yet the mesencephalic structures were undamaged. The cerebral hemispheres, basal ganglia, thalamus, and medulla oblongata were normal; the cerebellum appeared a little small. Except for cystic change, the pineal body was not remarkable.

Microscopic sections were prepared with hematoxylin-eosin, Mallory's phosphotungstic hematoxylin, Weil's myelin stain, and Hortega's silver carbonate stain (figure 6A-C). The lesion showed no sharp demarcation at its base near the left mammillary body. The structure of the mass was uniform; it consisted of a dense network of glial fibers with sparsely interspersed mature fibrillary astrocytes and a few scattered, well differentiated ganglion cells, mostly of small or medium size. Scanty myelinated nerve fibers transversed the lesion, some of them in bundles. Cranial nerves and larger blood vessels passed intact through tunnel-like structures. The exact histologic classification of this lesion proved to be difficult. It was considered a transitional form between a heterotopic hyperplastic malformation (hamartoma) and a true dysontogenetic glioneuronal neoplasm. The size of the mass and its predominantly fibrillary-astrocytic structure certainly suggest fully differentiated glioma, yet the complete maturity of its components and the lack of invasive properties are traits which resemble a malformation.

Case 2. A boy was born on October 3, 1953 of a normal spontaneous primiparous delivery. The parents noted a deep voice at birth, the fact that he was always larger than other children of the same age, and that by the age of three months his penis was enlarged and subject to frequent erections. At the age of one year he began to delight in the company of older females; he would

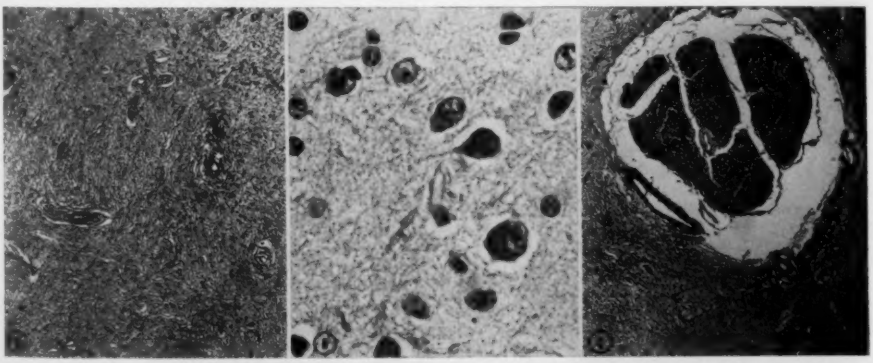

FIG. 6. *Case 1*. *A*, histologic appearance of lesion at low magnification, demonstrating an acellular astrocytic area. *B*, area containing well defferentiated ganglion cells. *C*, intact cranial nerve tunnelling through tumor.

try to stroke their skin. He had never done this with males. When seen by a physician in Chattanooga, Tennessee on May 16, 1955, at the age of 19 months, his height was 91.5 cm. and he weighed 16.3 kg. The blood count was normal. The blood sugar was 110 mg. per cent, cholesterol 147 mg. per cent, and 17-ketosteroids on three occasions ranged from 0.6 to 2.2 mg. in 24 hours.

He was admitted to Henrietta Egleston Hospital, Atlanta, Georgia and examination showed a two and one-half year old boy who looked at least five years of age (figure 1B). Acne was present over the shoulders, with numerous comedones over the bridge of the nose and upper cheeks. The lower teeth were widely spaced. The genitalia were those of a normal 12 to 14 year old male, with large firm testicles, heavy dark pubic hair, and a sizable penis. The extremities were heavily muscled, particularly the legs. The bones were large and the hands broad. General and neurologic examinations revealed normal fundi, symmetric power, sensation, and reflexes. The mental activity seemed normal for his age, although he rumbled baby-talk in a resonant bass voice. No abnormal abdominal mass could be felt. Blood sugar was 81 mg. per cent, nonprotein nitrogen 26 mg. per cent, and urinary 17-ketosteroids were 2.3 mg. in 24 hours.

After being examined by one of the authors, the patient was transferred to Crawford W. Long Hospital, Atlanta, Georgia on April 3, 1956. The height was 107 cm., the weight 21 kg. Roentgenograms at this time showed a bone age of six to seven years. Pneumoencephalography revealed an abnormal soft tissue mass 2 cm. in diameter in the interpeduncular space, slightly elevating the third ventricle (figure 3B). Spinal fluid examination was normal, with a total protein of 27 mg. per cent. On rectal examination the firm and symmetric prostate gland measured 3 by 3 by 1 cm. and, on massage, yielded normal prostatic fluid without spermatozoa.

The patient was readmitted to Crawford Long Hospital on September 8, 1956. His over-all height was then 114.5 cm., crown-rump height 67 cm., and head circumference 52.5 cm.

It was decided to explore the lesion. A large right osteoplastic flap was turned. With the head hanging down, the tentorial surface was followed after dividing one of the lateral temporal veins and a fairly good view of the interpeduncular cistern was obtained. There was an abnormal mass behind the pituitary stalk measuring more than 1 cm. in diameter. It had the color of normal brain tissue and was covered by numerous tiny arterioles. A biopsy was taken from the anterior aspect of the lesion, just behind the carotid level; here the tissue was soft and vascular and a single blood vessel had to be clipped. A second biopsy specimen of 4 mm. was taken from the posterior, much tougher, portion of the mass, with venous oozing ensuing.

The patient's immediate postoperative condition was good, except for a right-sided third nerve paralysis. On the following day, however, he began having focal left-sided convulsive seizures, starting in the face and fingers. These continued to be so troublesome that on the same evening the wound was reopened, but no subdural or extradural blood was found. No further convulsions occurred thereafter. Postoperative roentgenograms showed a clip at the level of the anterior clinoids and a centimeter to the right of the midline.

Microscopic preparation of the biopsy material stained with hematoxylin and eosin showed a fairly normal appearing cerebral substance containing glial cells and larger stellate elements possessing the characteristics of ganglion cells.

The glial cells were well differentiated, with little variation in nuclear size, shape, and staining character; in some areas they tended to form palisades, but this configuration was not neoplastic. Throughout there was an increased vascularity, with endothelial-lined vessels presenting congeries of spaces in some areas.

The histologic diagnosis was hamartoma.

The third nerve paralysis had improved when the patient was discharged October 1, 1956 and had entirely cleared by November 7, 1956.

On January 25, 1957, at the age of three years and three months, the height was 118 cm., crown-rump height 67.5 cm., and head circumference 52.3 cm. The lower central incisors had already been lost and the remaining milk teeth were more widely separated. Neurologic examination was entirely normal.

An electroencephalogram on January 25, 1957 showed a dysrhythmic activity on the right side. Background activity was principally 6 to 8 per second, with some low-voltage fast frequencies. There was a moderate degree of random 4 to 6 per second activity from the right side which spared the occipital region fairly well. No well-localized phases were recorded. Cooperation throughout the procedure was poor. It was concluded that the electroencephalographic changes could well have been postoperative and due to surgical trauma.

Since patients with lesions of this type have rarely survived beyond the teens, a 3,500 to 4,000 r tumor dose of deep roentgen therapy was given in March 1957. On May 6, 1957 his height was 125 cm., crown-rump height 73 cm., and head circumference 53.0 cm. The family reported that he was much more tractable. He had lost his upper central incisors and the lower central permanent incisors had erupted.

REVIEW OF CASES FROM THE LITERATURE

For the sake of comparison, the verified cases from the literature are reviewed here:

Case 3. Case of LeMarquand and Tozer (1934).[3] A two and one-half year old boy is described with marked physical overdeveloped ("Hercules type") macrogenitosomia and psychosexual prematurity. Death occurred at four years from endocarditis.

Autopsy showed a pedunculated mass 13.5 by 8 mm. attached to the right mammillary body and hanging free into the interpeduncular space. It consisted of "brain tissue" with differentiated neurocytes and myelinated nerve fibers imbedded in a matrix of fibrous glia. The hypothalamus, pineal, and pituitary were intact.

Case 4. Case of Driggs and Spatz (1940).[8] A boy, age two and three-quarter years, showed precocious physical and sexual development. He looked like a seven year old, with a bone age of 15 to 16 years and the height of a nine year old boy. Testicular development corresponded to 17 years, but his mental age was only that of three years. His blood pressure was 125/75. Neurologic and spinal fluid examinations were normal, as was the pneumoencephalogram. He died after laparotomy for suspected adrenal tumor.

Autopsy revealed a pedunculated mass about the size of a cherry pit, attached to the tuber cinereum. Histologically it was considered a hyperplastic malformation (hamartoma) containing nerve cells imbedded in glial tissue. The larger neurons were of the type seen in the infundibulomammillary nucleus and small nerve cells of the type found in the tuber cinereum (figure 7). There were also free-ending nerve fibers. The hypothalamus was undamaged. The pituitary, adrenals, and pineal were normal; the testes showed spermatogenesis.

Case 5. Case of Bronstein, Luhan, and Mavrelis (1942).[3] A 22 month old girl exhibited overgrowth (99 cm.), overweight (12.7 kg.), and precocious puberty (breast and pubic hair development, vaginal bleeding). The urine contained no estrogens, gonadotropin, or pregnandiol. Neurologic examination and pneumoencephalography were normal and exploratory laparotomy was negative. Death occurred from meningitis.

Autopsy disclosed a globular hamartoma of 4 mm. diameter in the midline between mammillary bodies and tuber cinereum; it contained ganglion cells of the type encountered in the tuber cinereum, a few myelinated nerve fibers, and a glial stroma. The pineal and pituitary were intact.

Case 6. Case of Hooft, Dietrickx, and Cieters (1943).[4] A girl, age two years, presented accelerated growth (bone age 6 to 8 years), precocious puberty (pubic hair, breast development), and polyphagia. Convulsive seizures without loss of consciousness had occurred since the age of seven months. She was mentally retarded. Death ensued from intercurrent disease.

At autopsy a small pedunculated heterotopic mass was seen to arise from the left mammillary body; it consisted of brain tissue. The hypothalamus, pineal, and pituitary were normal.

Case 7. Case of Seckel, Scott, and Benditt[5]—also described by Wilkins, (1950),[6] and by Richter (1951).[7] A girl, age seven years, with excessive growth (147 cm., 44.7 kg.) had adolescent breasts, axillary and pubic hair, and hypertrophied external genitalia; precocious puberty had started at two and one-half years, with menstruation at three years. The skeletal age was 14 to 17 years, but her dental and mental ages corresponded to the chronologic age. Neurologic examination was normal. Urinary 17-ketosteroids and estrogens were normal and pregnandiol was absent. Death followed negative exploratory laparotomy.

The anatomic findings of this case have been described in detail.[7] There was a pedunculated lesion 10 by 7 mm. attached to the posterior tuberal region and right mammillary body. The mass was a true hamartoma containing in a glial matrix five different ganglion cell types corresponding to normal hypothalamic nuclei. No evidence of neurosecretion was found. A bundle of myelinated nerve fibers connected the lesion with the hypothalamus.

Case 8. Case of Brouwer and Brummelcamp (1948).[8] A 20 year old male presented the syndrome of precocious puberty, polydactyly, epilepsy, and mental deficiency. Autopsy revealed a small, retroinfundibular mass containing ganglion cells. The tuber cinereum was damaged.

Case 9. Case of Stutte (1950).[9] A four year old girl began to have petit mal attacks at the age of ten weeks, precocious puberty at one year, and menses at two years. At first her mental development was premature, but she deteriorated after three years. Blood pressure was 125/70 to 135/80. Her gait was ataxic and speech dysarthric. She was agitated, aggressive, and showed progressive dementia. Pneumoencephalogram revealed upward displacement of the third ventricle. At five and one-half years she looked like a child of 12 years. Death occurred from scarlet fever.

Autopsy showed a plum-sized mass arising from the posterior part of the hypothalamus. It consisted of mature glia, ganglion cells (of the type found in the tuber cinereum and in the tuberomammillary nucleus).

Case 10. Case of Meyer (1948).[10] A three year old girl with overdevelopment (bone age five), obesity, precocious puberty, exhibited agitated behavior, mental retardation, and convulsive attacks. Menstruation started at the age of eight. She died at 13 years from pneumonia.

At autopsy there was a large hypothalamic mass arising from the tuber cinereum. The acellular growth contained glial tissue, ganglion cells, axis cylinders, ependymal tubes, and calcifications. There were extracellular and intracellular globules of secretion suggestive of "neurosecretion."

Case 11. Case of Stotijn and Nauta (1950).[11] A six year old boy developed petit mal and grand mal convulsive seizures at the age of four years. He exhibited rapid growth and macrogenitosomia, maniacal behavior, and mental deterioration. There were no neurologic changes except for irregular pupils and unsteady gait. The pneumoencephalogram was normal. Estrogens were increased. He died of pneumonia at the age of ten and three-quarter years.

At autopsy a large posterior hypothalamic mass was found to arise from the left mammillary body, consisting of mature glial tissue, nerve fibers, and

ganglion cells. This was diagnosed as a hamartoma. The posterior hypothalamic nuclei, the dorsomedial and centromedial nuclei, the forebrain bundle, and the thalamo-hypothalamic fibers were damaged on the left side.

Case 12. Case of Gross (1940).[12] A two year old girl showed increased bone growth, breast development, and beginning menses. Estrogens were increased in the urine.

Autopsy revealed an astrocytic hamartoma of the posterior hypothalamus.

Case 13. Case of Weinberger and Grant (1941).[13] A seven year old boy with precocious puberty exhibited mental dulling, bilateral papilledema, vertical nystagmus, and slight ataxia. Urinary estrogens were normal, gonadotropins negative. A hypothalamic tumor was demonstrated by ventriculography and subsequently verified surgically. It was then considered to be an astrocytic glial malformation rather than a true neoplasm. The patient lived to age 12.

At autopsy the tumor was described as being well encapsulated, cystic to palpation and was diagnosed as a fibrillary astrocytoma, type two.

Case 14. Case of Vickers and Tidswell (1932).[14,15] An eight year old boy showed precocious puberty since the age of three, convulsions since four years, and violent maniacal behavior changes since his sixth year. Neurologic examination was normal.

At autopsy a mass was found which originated from the infundibulum and mammillary bodies and budged into the lumen of the third ventricle. It was described as "astrocytoma," but no accurate histologic information was given.

Case 15. Case of LeGros, Clark, Riddoch, Beattie, and Dott (1936).[16] An eight year old girl with precocious puberty had convulsive attacks since birth. After the age of six months the attacks were initiated by an aura of laughter. There were no neurologic or mental changes.

Autopsy showed a large, presumably congenital tumor arising from the tuber cinereum and mammillary bodies. This was designated an astrocytoma, but no histologic details were given.

Case 16. Case of Horrax and Bailey (1928).[17] A seven year old boy with precocious puberty since the age of three and excessive physical development (height 142 cm., weight 50 kg., bone age 18) developed headaches and diplopia. There were bilateral papilledema and paresis of the right sixth nerve. Roentgenograms of the skull showed a dense suprasellar calcification. Death ensued after attempted removal of the lesion.

At autopsy, a large, presumably congenital tumor was present, attached to the floor of the third ventricle and partially occluding it. The lesion was composed of glial and nerve cells and myelin sheaths. Calcifications were abundant. The histologic diagnosis was "ganglioneuroma."

ANATOMIC ASPECTS

Certain morphologic and neurophysiologic aspects of these cases raise questions of fundamental importance which merit additional comment. Surprisingly small lesions were seen in cases 2, 4, 5, 6, 7, and 8, measuring from a few millimeters to 2 centimeters in diameter. All of them were pedunculated growths resembling a collar button in size and shape. They were attached to the posterior hypothalamus between the tuber cinereum and the mammillary bodies and mushroomed into the interpeduncular cistern. Many of the larger lesions still showed the same arrangement (cases 1, 3, 9, 10, 11), filling the space between chiasm and pons and, in some instances, tending to bulge into the cavity of the third ventricle. In none of these, however, was there any attachment to, or infiltration of, the brain except at their sessile base in the tuberomammillary region. Thus far, no embryologic explanation for such preferential location is evident. Their peculiar shape suggests slow unimpeded growth into the free subarachnoid space. No direct invasion or severe displacement of cranial nerves and basilar blood vessels has been observed. The hypothalamic nuclei and fiber tracts were completely undisturbed in the smaller lesions, but larger masses caused local destruction by direct compression.

Controversy exists among pathologists as to whether these lesions should be classified as malformations or neoplasms. Richter[7] insisted that the term hamartoma (hyperplastic heterotopia) had been used too loosely in cases which were actually tumors. Unfortunately, some of the earlier reports lack sufficient detail to permit one to make an accurate histologic diagnosis (cases 14 and 15). In our opinion, there are transitional forms between malformation and neoplasm. The smaller lesions invariably have the appearance of heterotopic hyperplastic malformations, that is, a true hamartoma (figure 7). A fibrous glial matrix contains scanty mature glial cells, clusters of mature ganglion cells, and sparse myelinated nerve fibers. The neurons are identical to those found in the normal hypothalamus; for example, the magnocellular elements correspond to cells of the tuberoinfundibular nucleus and the smaller ganglion cells to those of the nucleus of the tuber cinereum. Although the myelinated fibers sometimes form bundles, they seem to make no connections with normal anatomic structures. On the other hand, the larger lesions resemble more dysontogenetic neoplasms, yet in spite of their site and tumorlike prevalence of certain tissue elements, they exhibit no infiltrative tendency and their cellular constituents usually are fully differentiated. In

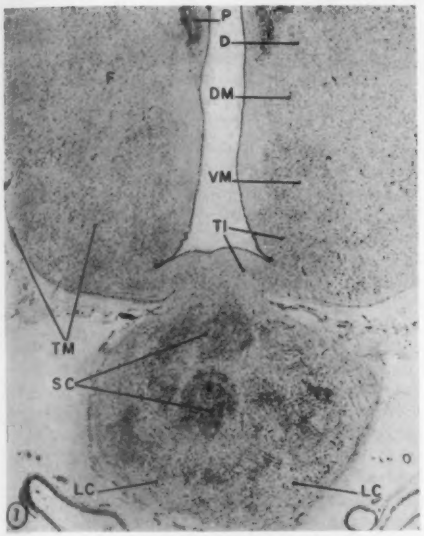

FIG. 7. Microscopic preparation of hypothalamic hamartoma (case of Spatz and Driggs). Courtesy of Dr. Webb Haymaker, Armed Forces Institute of Pathology, Washington, D. C.

case 10 there were mature neurons and astrocytes, monstreglial cells, ependymal tubes, areas of calcification, and, in addition, intracellular and extracellular globules suggestive of "neurosecretion." Cases 12 and 13 were classified as astrocytomatous malformation and our own case 1 also showed preponderance of areas resembling a fibrillary astrocytoma. On the other hand, in case 16, because of an abundance of the ganglionic elements, Bailey and Horrax termed the tumor a "ganglioneuroma."

CLINICAL ASPECTS

These lesions appear to be almost equally divided between the sexes. Since symptoms occur early in life and sometimes almost immediately after birth, one is immediately suspicious of a dysontogenetic nature. Most patients lived only to the early portion of the second decade.

Certain characteristic clinical signs are common to most of the cases under discussion: 1) physical overgrowth and sexual precocity, 2) convulsive disorder, 3) mental changes, and 4) absence of gross neurologic changes.

1. The outstanding feature of this group, excessive physical growth and sexual precocity, may be seen as early as in the second year. Premature development does not affect all aspects of growth equally. Bone age as determined by roentgenogram is far ahead of chronologic age; hence these children are well advanced in height and weight. On the other hand, dental age is not accelerated. Precocious puberty is always isosexual, with secondary sex characteristics (development of external genitalia, breasts, and pubic and axillary hair) preceding and proportionately surpassing the growth of the gonads, uterus, and prostate. Premature menstruation occurred in some instances. Mental precocity is rarely present; in fact, the mental performance usually falls behind normal. Premature psychosexual reactions are uncommon (cases 2 and 3). Progressive obesity is apt to be present in the later stages.

2. As a rule, the convulsive disorder occurs early and may begin shortly after birth. The attacks are described either as brief lapses without complete loss of consciousness or as short tonic seizures with occasional signs of lateralization. In some cases phenomena suggestive of diencephalic discharge have been observed, such as paroxysmal laughter or giggling (cases 1 and 15) or paroxysmal pallor and blushing. Convulsive phenomena seem to be more often associated with larger lesions.

3. Mental changes consist of behavior disorders, abnormal affective responses, and intellectual deterioration. Emotional lability, mischievousness, and agitation are common. Some patients show violent outbursts of temper; for example, case 14 exhibited "sham rage" at the slightest provocation. After normal earlier development, the psychic disturbances occur at a late stage of the disease and are usually associated with large lesions.

4. Malformations, even when they encompass the second, third, and sixth nerves, produce little, if any, neurologic deficit. A mild ataxia and nystagmus in some cases did suggest pontine compression. A syndrome of increased intracranial pressure was noted only in cases 13 and 16, apparently because here the bulk of the mass had extended upward and occluded the third ventricle.

ROENTGENOLOGIC ASPECTS

Since these lesions protrude into the subarachnoid space of the interpeduncular cistern, they can be demonstrated by pneumoencephalography. As a rule, the interpeduncular cistern is well shown on the lateral pneumoencephalogram; it is limited anteriorly by carotid arteries, optic chiasm, and infundibulum.

posteriorly by the ventral surface of the pons, and superiorly by the hypothalamic structures of the tuberomammillary region and the cerebral peduncles. The basilar and posterior cerebral arteries and third nerves are sometimes seen crossing the cistern, and the normal mammillary bodies may be identified by a slight bulge in the floor of the third ventricle. Tiny tumor masses arising from the tuberomammillary region may escape detection or give a picture indistinguishable from an incompletely filled normal interpeduncular cistern (filling only the superficial but none of the deep interpeduncular portion). The mass in case 2 was clearly outlined by the remaining air in the cistern. The large mass in case 1 produced gross distortion by elevating the floor of the third ventricle and displacing brainstem and aqueduct posteriorly (figure 3A and B).

NEUROPHYSIOLOGIC CONSIDERATIONS

The pathogenesis of precocious puberty by central nervous system lesions has evoked much speculation. The earlier concept of pineal tumors as a cause has been abandoned. Harris,[18] Green,[19] Bustamente,[20] and DeLange[21] have presented convincing experimental and clinical evidence that lesions of the posterior hypothalamus, especially in the region of the tuber cinereum, are responsible for this disorder. Even though the hypothalamic lesion may be the primary cause of precocious puberty, the peripheral manifestations of this syndrome must be due either to gonadal hyperactivity or to excessive pituitary gonadotropic stimulation. It is noteworthy that in every case which was adequately studied, the gonads, pituitary gland, and adrenals were found to be anatomically normal. Several theories have been proposed to explain the functional relationship between hypothalamus and the target glands.

According to one unproved hypothesis, the posterior hypothalamic lesion gives rise to neural impulses which reach the gonads through descending autonomic pathways and render them over-reactive to the normal circulating gonadotropine. More likely, the hypothalamic influence on sex characteristics is mediated by the anterior lobe, indirectly by release of gonadotropin. Thus far, the mode of interaction between the hypothalamus and adenohypophysis is not clear; at any rate, no direct neural connections have yet been demonstrated between these structures.[18,19] Grant and Weinberger[13] postulated an inhibitory effect of the posterior hypothalamus on pituitary activity and thus interpreted precocious puberty associated with destructive lesions of the posterior hypothalamus as a release phenomenon. However, this assumption fails to explain cases in which a small hamartoma left the hypothalamic structures perfectly intact.

The observed facts appear to be better explained by the theory of neurohumoral transmission.[18,19] Neural impulses from the normal tuberal nuclei liberate a chemical substance which is carried by the portal vascular system of the pituitary stalk to the anterior lobe, thereby releasing gonadotropin. If a lesion in the posterior hypothalamic area mechanically interferes with the hypophyseal-portal circulation or causes qualitative or quantitative changes of metabolites carried by this circulation, an excessive release of gonadotropin may result.[11] The mere presence of a posterior hypothalamic lesion does not itself cause precocious puberty. To some extent the development of this syndrome appears to depend upon the histologic character of the lesion; for example, precocious puberty is frequently found with masses of neural (ganglionic and/or glial) origin, but not so with other tumors of similar location (craniopharyngioma). Since hamartomas and gangliogliomas of this region contain functioning ganglion cells, they constitute an actual increase of the total hypothalamic cell mass and, therefore, may be responsible for a functional exaggeration of tuberohypophyseal activities. Driggs and Spatz[2] theorized that hamartomas actually possess neurosecretory function and are capable of liberating directly excessive amounts of gonadotropin. There is, however, no histologic proof for the latter theory and in only one case[10] were intracellular inclusions found suggestive of "neurosecretion." Another argument against the theory of Driggs and Spatz is that precocious puberty may be associated with destructive lesions of the hypothalamus. Such lesions should reduce the number of functioning hypothalamic cells and thus diminish the amount of secreted gonadotropin.

The occurrence of convulsive disorder and mental changes in hamartoma and ganglioglioma is too frequent to be regarded as merely coincidental. The seizure pattern resembles remarkably that seen in petit mal and subcortical tonic seizures. The attacks are likewise frequently accompanied by paroxysmal laughter or crying or vasomotor signs suggesting diencephalic origin. According to current neurophysiologic concepts, petit mal is initiated by a central pacemaker mechanism in the di-

encephalon and rostral portion of the mesencephalon. Lesions in this area are known to interfere with the ascending activating systems and to produce profound disturbances of the electric activities of the brain. Since the seizures are more common in larger lesions and since these encroach on hypothalamus and upper midbrain, it seems justified to postulate that the attacks and abnormal electric discharges are focal in nature and caused by local irritative effect of the lesions.

Psychic disturbances in these patients may also have a focal basis. Sham rage has been observed in the destructive lesions that release the autonomic activities of the posterior hypothalamus and also in irritative lesions of the limbic system (especially of the amygdaloid complex). The limbic system is intimately connected with the hypothalamus, the mammillary bodies representing an important relay station. Larger lesions attached to the posterior hypothalamus doubtless interfere with the function of mammillary bodies and their connections and may also mechanically irritate the amygdaloid region, thus giving anatomic explanation for abnormal affective responses. The question arises whether or not the psychic changes can be correlated to the profound disruption of electric activity.

THERAPEUTIC ASPECTS

The problem of treatment of posterior hypothalamic hemartoma must be discussed. Surgical removal should be effective, if feasible. In cases 13 and 16 large tumors were approached by transventricular operation from above; this procedure carries a high mortality and does not permit total removal. In case 2 a surgical approach similar to that for peduncolotomy presented limited visibility, but the lesion could be differentiated from the surrounding structures. Bleeding from tiny arterioles as well as deep venous bleeding made its removal impossible, yet an adequate biopsy was obtained.

Since the lesions under consideration are composed of mature neural and glial elements, they are not likely to be radiosensitive.

On the other hand, if one assumes that precocious puberty is the functional expression of an increased cell mass in the posterior hypothalamus, radiation therapy may conceivably be of value by inhibiting such cellular activity. Irradiation was tried in case 2, but the period of observation has been too short for final evaluation.

SUMMARY

The hamartoma and the ganglioglioma of the posterior hypothalamus represent a well defined clinicopathologic entity.

Anatomically, they are related dysontogenetic conditions. The hamartoma is merely a heterotopic hyperplastic malformation, whereas the ganglioglioma is a fully differentiated neoplasm, but there exist transitions between these groups. These lesions form pedunculated masses which arise from the tuber cinereum or the mammillary bodies, but do not invade neighboring structures; they are composed of mature ganglion cells, nerve fibers, and glial elements.

Clinically, the hamartoma and ganglioglioma of the posterior hypothalamus are characterized by a typical syndrome: 1) isosexual precocious puberty and advanced somatic growth; 2) convulsive disorder, suggestive of diencephalic origin, with electroencephalographic changes at times resembling petit mal; 3) mental disturbances, especially involving the affective responses; and 4) absence of abnormal neurologic findings. They cause symptoms in early childhood, often shortly after birth.

Roentgenologically, the lesion may be shown by pneumoencephalography as an abnormal soft tissue mass in the interpeduncular space.

Neurophysiologically, these lesions pose interesting problems regarding the pathogenesis of precocious puberty and the mechanism of convlusive and mental disorder. It is suggested that in these cases convulsions and mental changes are of focal (hypothalamic) origin.

Therapeutically, another surgical effort at cure of such a lesion was unsuccessful. The ultimate effect of radiation therapy will have to be uncovered with time.

Two personal observations are reported in detail, one with autopsy, a second with biopsy, and additional cases from the literature have been reviewed.

We are indebted to Dr. W. W. Dickerson, Caro, Michigan, for clinical follow-up reports and to Dr. S. C. Capps, Grand Rapids, Michigan, for the general autopsy findings in case 1.

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■ Before I speak of the several classes of symptoms in cases of intracranial tumours and other kinds of adventitious products, I have to make a statement which may surprise some of you. It is that occasionally *there are no symptoms* in these cases. And frequently when symptoms are present they are insignificant in comparison with the size of the tumour found post-mortem, or, more correctly speaking, in comparison with what we might theoretically infer from the size of the tumour. But I say "post-mortem"? Well, it is a fact that a patient will *die* without cerebral symptoms—die of non-cerebral disease—and yet an adventitious product will be found within his cranium; or he may die suddenly in the midst of apparent good health, and we find an adventitious product of some standing.

J. Hughlings Jackson in *Lectures on the Diagnosis of Tumours of the Brain*, published in 1872.

Collateral regeneration in partially denervated muscles

Gunnar Wohlfart, M.D.

In 1945 three different groups of American scientists[1–3] reported that partially denervated muscles in experimental animals show a remarkably rapid recovery of muscle strength, even in the absence of regeneration of the severed axons. Other authors confirmed this observation in the following years, and demonstrated histologically that the recovery in strength is due to reinnervation by collateral branches from surviving motor nerve fibers.[4–7]

It was thought for some time that collateral branching of residual nerve fibers occurs only in the muscles and not in the extramuscular parts of the muscle nerves. However, in 1955 Causey and Hoffman[8] demonstrated by use of electron microscopy that numerous thin collaterals are formed along the whole neuron distally from the level of the injury. The reinnervation of denervated muscle fibers is produced mainly by collaterals formed within the muscle, obviously because these have the shortest distance to grow to come into contact with muscle fibers.

The collateral sprouts enter the Buengner bands formed from degenerating nerve fibers and follow these bands to the muscle fibers. Usually the old end-plates are reinnervated. When an end-plate has been reinnervated, it will, as a rule, not receive a second sprout but exceptions from this rule are not so uncommon. Doubly innervated end-plates may then be observed.

As yet, nothing is known about the fate of those collaterals originating more proximally in the nerve trunks. One possibility is that they are finally absorbed; another is that they remain in the nerves but unconnected in the periphery. As a matter of fact, this is the same problem that has been discussed many times concerning ordinary nerve regeneration following an injury. It is well known that out-growing sprouts are produced in excess, but the fate of these excess fibers is unknown. Gutmann and Young[9] felt that there might be a gradual absorption of these fibers, but they could produce no definite evidence.

The histologic findings in collateral regeneration are, in all essential details, analogous to those found in common "terminal" nerve regeneration. This regeneration was described half a century ago by Cajal and his contemporaries. The principal difference between collateral and terminal regeneration is the fact that collateral sprouts are formed from intact nerve fibers lying close to degenerating ones, while terminal sprouts have their origin in an interrupted fiber, the proximal part of which is preserved.

Wohlfart and Hoffman[10] studied Theiler's encephalomyelitis in mice (so-called mouse poliomyelitis). This disease is analogous to human poliomyelitis in all respects. Surviving animals recover more or less, but permanent paralysis and wasting of certain muscles or parts of muscles are often found. One hundred and twenty-five mice with Theiler's encephalomyelitis were examined. For comparison, traumatically induced collateral sprouting was studied in 16 mice. It was concluded that collateral regeneration from surviving motor nerve fibers must be of considerable importance for the recovery of paralyzed muscles in Theiler's disease. Collateral regeneration was regularly found in partially denervated muscles from the ninth day on after paralysis. Occasionally some sprouts were found earlier, but the impression gained was that collateral regeneration was significantly delayed in comparison with conditions in traumatically induced collateral sprouting in mice. Following partial denervation by crushing of the sciatic nerve in the gluteal region, some sprouting from the surviving fibers was regularly seen

From the University Hospital, Lund, Sweden.
Robert Wartenberg memorial lecture, presented at the ninth annual meeting of the American Academy of Neurology, Boston, April 1957.

four to five days after the operation and collateral regeneration was striking six to seven days afterward.

Electron microscopy of the sciatic nerve revealed that the formation of submicroscopic collaterals started as early in mouse poliomyelitis as in the operated animals. Since these collaterals must reach a certain minimum diameter before they can be recognized in the light microscope, it seems plausible to assume that maturation is delayed in mouse poliomyelitis. This may have something to do with reversible changes in the surviving ventral horn cells. Such changes are common in the first week after the onset of paralysis. It is probable that such cells, which are usually in a state of chromatolysis, cannot produce substances necessary for the maturation of the collateral sprouts.

When intramuscular sprouts are first seen in the light microscope, they have usually already achieved connection with end-plates. They are very thin at first (about 0.5 micron) and lack Ranvier nodes. The recently reinnervated end-plates stain less heavily with gold than normal plates, but usually they contain several intensely stained dots. Only occasionally does one see sprouts ending with a small knob or ring. It seems reasonable to assume that the reestablishment of contact with the end-plates usually occurs in the submicroscopic stage.

Many sprouts arise far distally in the muscles, usually from Ranvier nodes of surviving motor nerve fibers. Others are obviously formed at more proximal levels.

During the first month of paralysis the majority of the new-formed collaterals mature and gradually assume the appearance of normal nerve fibers. In normal mouse muscles the terminal innervation ratio, that is, the number of end-plates in relation to the number of nerve fibers in the terminal motor bundles, will only slightly exceed 1:1. Following Theiler's disease this ratio may reach values as high as 5:1. Such findings clearly indicate previous collateral regeneration.

Wohlfart and Hoffman observed that some collateral sprouts were extremely thin even up to 200 days after the paralytic stage. In view of experience gained in material from human poliomyelitis cases, it was considered desirable to study the later stages of mouse poliomyelitis in greater detail. Therefore, a further group of ten mice was inoculated with Theiler virus. These animals were killed two to eight months after the induction of paralysis. Some immature sprouts were always found. Many of these sprouts reached end-plates, while others terminated with a knob. Immature sprouts were also found in the extramuscular parts of the nerves.

We are now arriving at the problem whether and, if so, to what extent collateral regeneration occurs in human muscles. The occurrence of collateral regeneration from residual motor nerve fibers in human material was demonstrated[11] at the 1954 German neurologic congress in Würzburg and independently by Coers.[12] Later on Woolf[13] reached the same conclusion.

In a recent paper[14] amyotrophic lateral sclerosis was analyzed, and it was pointed out that signs of nerve regeneration are regularly found in this disease. Certain clinical consequences were also discussed.

Collateral regeneration is abundant in amyotrophic lateral sclerosis and has the same microscopic appearance as in experimental animals. Under normal conditions terminal motor nerve fibers in human muscles are connected with one or occasionally two end-plates. Coers demonstrated by his vital methylene blue method that single nerve fibers in amyotrophic lateral sclerosis may innervate several end-plates as a result of collateral regeneration. The methylene blue method is very good for this purpose, and and increased number of end-plates per terminal motor nerve fiber is often seen (figures 1 and 2A). The same can be shown by supravital gold impregnation. This latter method can also be used to visualize the relationship between out-growing collaterals and neurilemmal tubes, as well as for studies on the diameter and maturation of collateral sprouts (figure 2*C*). Silver methods are suitable for similar purposes, but the topography of fibers and end-plates cannot be studied as well because of the necessary thinness of the sections. However, silver impregnation is the only possible method for autopsy material. Methylene blue and gold can only be used for biopsies.

In amyotrophic lateral sclerosis there is ob-

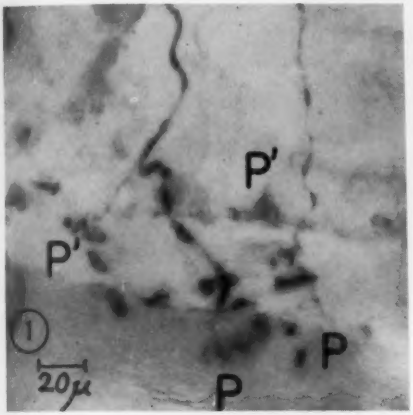

FIG. 1. Woman aged 56. Amyotrophic lateral sclerosis. Biopsy from the vastus medialis. Vital methylene blue method of Coers. The figure shows two motor nerve fibers running to end-plates (P), both giving collaterals to end-plates (P') in adjacent muscle fibers.

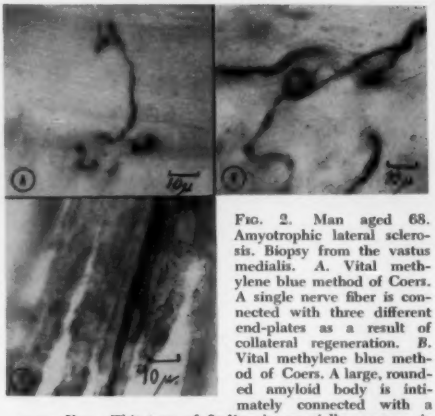

FIG. 2. Man aged 68. Amyotrophic lateral sclerosis. Biopsy from the vastus medialis. *A.* Vital methylene blue method of Coers. A single nerve fiber is connected with three different end-plates as a result of collateral regeneration. *B.* Vital methylene blue method of Coers. A large, rounded amyloid body is intimately connected with a nerve fiber. This type of finding is especially common in amyotrophic lateral sclerosis. *C.* Supravital gold impregnation (Löwit method). Five terminal neurilemmal tubes are seen. Only one of the tubes contans a normal nerve fiber. A thin collateral sprout is running with the second tube from the left. This method gives the most accurate information about the caliber (and thus the degree of maturation) of the sprouts.

viously a conflict between degenerative and regenerative powers. This must retard the course of the disease considerably. Collateral sprouting can be demonstrated regularly in biopsies from fasciculating muscles, even in the absence of weakness and wasting. An interesting observation is the fact that immature collaterals (figure 2*C*) and neuromuscular junctions always seem to be present in fasciculating parts of a muscle. This observation may be of importance for the explanation of the fasciculation phenomenon.

Terminal knobs (growth-cones), as well as knobs and irregular swellings in the course of the nerve fibers, are constantly found in amyotrophic lateral sclerosis (figure 3). These knobs and swellings are of the same type as those described by Cajal[15] and others as indicative of nerve regeneration. In a great number of experiments with nerve lesions in different experimental animals, we studied under what circumstances such knobs and swellings appear (figures 3 and 4). It seems obvious that they appear when outgrowth of regenerating fibers is prevented or retarded. An interesting fact is that some of the larger knobs may be transformed into amyloid bodies (figure 2*B*).

In 1954 we pointed out that collateral regeneration is found in human poliomyelitis.[11] Coers[12] proved that this regeneration is very extensive. Collateral regeneration must, therefore, be considered in the discussion about different explanations for the spontaneous regression of palsies in surviving cases of this disease.

In recent studies we have found that immature collaterals are often found in great numbers in human poliomyelitis, even many years after the acute stage. This applies both to collaterals connected with end-plates (figure 5) and to those found within intra- or extramuscular nerve trunks (figure 6).

The problem of why many collaterals never mature cannot be definitely solved at present. Thin sprouts in larger nerve trunks are probably those which have not established any contact in the periphery. Concerning distally formed but immature collaterals, one possibility is that certain motor units may have increased so much in size by collateral regeneration that the corresponding ventral horn cells are incapable of producing sufficient amounts of substances necessary for maturation. Another possibility is that collaterals formed in extramuscular parts of the nerve trunks may successively reach denervated muscle fibers and lead to at least some degree of reinnervation. This would provide one possible

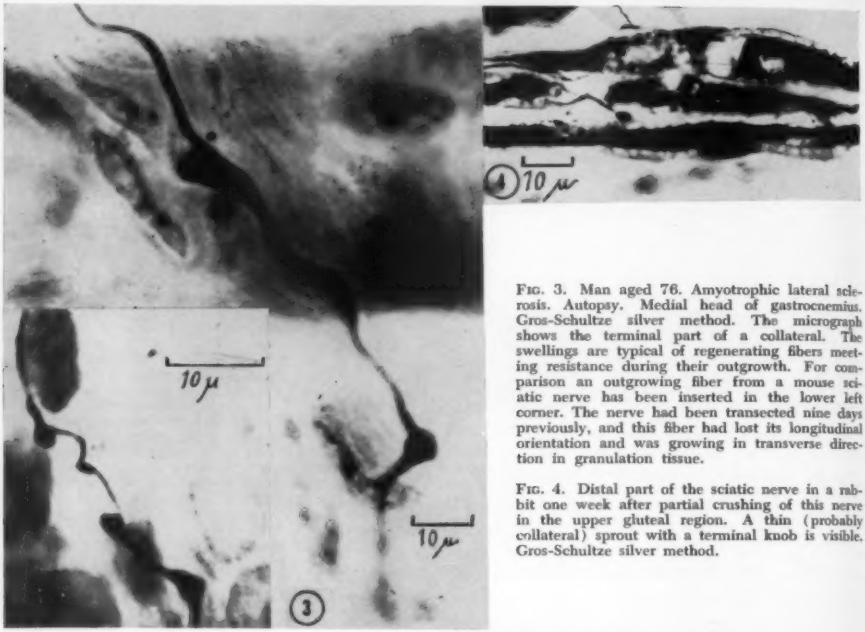

FIG. 3. Man aged 76. Amyotrophic lateral sclerosis. Autopsy. Medial head of gastrocnemius. Gros-Schultze silver method. The micrograph shows the terminal part of a collateral. The swellings are typical of regenerating fibers meeting resistance during their outgrowth. For comparison an outgrowing fiber from a mouse sciatic nerve has been inserted in the lower left corner. The nerve had been transected nine days previously, and this fiber had lost its longitudinal orientation and was growing in transverse direction in granulation tissue.

FIG. 4. Distal part of the sciatic nerve in a rabbit one week after partial crushing of this nerve in the upper gluteal region. A thin (probably collateral) sprout with a terminal knob is visible. Gros-Schultze silver method.

explanation of why poliomyelitis cases may improve to some small extent even several years after the acute stage.

Collateral regeneration is certainly of great importance in other human diseases as well. Every disease causing partial denervation of muscles can be expected to give rise to branching of residual motor nerve fibers and increase the size of remaining motor units. So far, signs of reinnervation have been found in syringomyelia, spinal root compression, and polyneuritis. In the last-mentioned type of disease, both terminal and collateral regeneration is seen.

The quantitative conditions in collateral regeneration are of special interest and will have to be studied further. In amyotrophic lateral sclerosis, where the affected ventral horn cells are usually scattered over wide areas, there are ideal conditions for collateral sprouting. We have examined several muscles and at the same time the corresponding muscle nerves in autopsies in this disease. In such studies one is often struck by the fact that a muscle region may appear normal or almost normal, but the corresponding nerve may be denervated to a considerable extent. It can be stated that at least one-third of the motor fibers of a given muscle may be destroyed and yet the muscle may be practically normal. This means that the mean size of the motor units has increased considerably. Similar observations have been made in human poliomyelitis, though the degree of muscular wasting may also appear proportional to the degree of nerve destruction.

The English orthopedic surgeon Sharrard[16] reported that the ventral spinal roots may be atrophic and the ventral horn cells destroyed to a great extent in old poliomyelitis cases, in spite of the fact that the corresponding muscle groups appear normal or only slightly wasted. This observation indicates an increased size of the remaining motor units caused by collateral sprouting.

Collateral regeneration must be of great importance for the interpretation of certain findings in clinical electromyography. On the other hand, electromyography as well as other electrophysiologic methods may contribute to the elucidation of problems concerned with

nerve regeneration. Together with Dr. Jörgen Fex, the author is investigating certain aspects of the correlation between electromyographic and microscopic findings in a given muscle region.

In the course of regeneration following a nerve injury, extremely polyphasic action potentials often appear. These may be regarded as evidence of reinnervation. They are explained by the small diameter of the outgrowing nerve fibers, which conduct slower than normally and by the immaturity of the end-plates, which may cause a delay in the neuromuscular transmission. The polyphasic potentials are successively being normalized, somewhat parallel with the microscopic maturation process.

In clinical electromyography one may find polyphasic potentials so early after a partial nerve injury that a direct outgrowth seems impossible. It is tempting to assume that such polyphasic potentials may be caused by collateral regeneration. In order to test this theory, we have partially denervated muscles of the hind legs in 24 rabbits. This denervation was produced in different ways, but the results to be reported here were obtained in rabbits, in which the sciatic nerve had been partially crushed at the highest possible level in the gluteal region. It was found in several instances that extremely polyphasic potentials, which do not occur normally in rabbits, could be registered from the fourteenth day on. The rabbits were not kept under any form of anesthesia.

It is known[7] that collateral regeneration is found in the rabbit, as well as in other experimental animals. In our series collaterals were found in the muscle from eight days on after the operation. The distance from the level of crushing in the sciatic nerve to the entrance of the muscle nerve was more than 8 cm. The speed of the direct outgrowth is 3 to 4 mm. a day, according to previous authors. It seems improbable that direct reinnervation could occur after only 14 days. Furthermore, a great number of collateral sprouts running to end-plates were found in the same muscle regions that gave polyphasic potentials. Thus, we feel that the theory has been verified that collateral regeneration may cause polyphasic potentials.

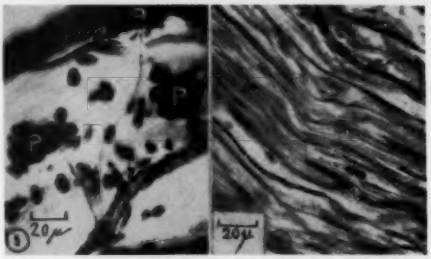

FIG. 5. Woman aged 33. Poliomyelitis two and a half years after the acute stage. Autopsy. Medial head of gastrocnemius. Gros-Schultze silver method. Three end-plates (P) are visible. The nerve fiber running to the end-plate to the left has sent a collateral to the end-plate in the uppermost part of the field.

FIG. 6. Man aged 34. Poliomyelitis six years after the acute stage. Autopsy. Silver impregnation. Ulnar nerve at the wrist. The number of large nerve fibers is considerably reduced. Several bundles of very thin nerve fibers are seen. These fibers are interpreted as being collateral sprouts.

It should also be pointed out that the increase in size of many motor units in partially denervated muscle probably explains the increase in duration and amplitude of action potentials in such muscles.

The occurrence of collateral regeneration in human beings must be considered established, and it seems probable that this phenomenon will prove to be of considerable clinical interest. Several problems must be studied further, however. The question as to what extent reinnervation by collateral regeneration is possible is one important point. Another is the problem of why new-formed collaterals may remain immature, for example, in poliomyelitis. Concerning poliomyelitis, it is of special importance to elucidate why the same muscle, which contains an excess of collaterals in the nerve trunks, may contain large areas of denervated muscle fibers.

Some further possibilities to explain clinical observations of different kinds by collateral regeneration will be suggested.

The restitution following partial peripheral nerve injuries is often much more rapid than would be expected from the known time conditions in direct outgrowth of interrupted nerve fibers. This restitution is probably partly a result of recovery of lesions, which have caused impairment of conduction properties in the nerve fibers without any degeneration of their distal part. Another possibility is collateral regeneration. That this mechanism is

of importance is suggested by electromyographic findings in partial nerve injuries. In such cases the amount of denervation activity is often surprisingly small and polyphasic potentials may appear before direct outgrowth can be considered possible.

In spinal root compression one is often struck by the fact that the resulting motor signs are relatively small. This might have to do with collateral sprouting.

Neurosurgeons are often surprised that no facial palsy or, if so, only very slight palsy is seen in neurinomas, though the facial nerve may be severely damaged by the tumor. An analogous explanation lies close at hand.

Other examples than those mentioned may be found easily.

SUMMARY

1. A brief review of our knowledge about collateral regeneration is given.

2. Surviving motor nerve fibers in partially denervated human muscles are capable of branching and reinnervation of adjacent denervated fibers.

3. Collateral regeneration may explain certain clinical and electromyographic phenomena in partially denervated muscles.

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■ The local means for promoting the recovery of the paralyzed muscles are certainly of not less importance than the general means, possibly of much greater importance, and these local means are very various. The efficacy of frictions and shampooings appears to be indisputable. The efficacy of proper movements can only be doubted by those who are unacquainted with the results arrived at by the "movement cure," and by systematic movements of one kind or another, with or without the help of mechanical apparatus. The efficacy of faradization has been abundantly proved, and there is good reason to believe that this is not the only mode of using electricity which will be of great service; that in fact statical positive electricity, or the interrupted galvanic current, or the application of the galvanic current in such a way that the paralyzed nerve is acted upon chiefly by the positive pole—a mode of using electricity about which I have spoken elsewhere, and which I have used extensively during the last three or four years—will often be of great service in proper cases.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

Osteoporotic kyphosis with paraplegia

Warren H. Kempinsky, M.D., Peter P. Morgan, M.D. and William R. Boniface, M.D.

Among the various causes of paraplegia, one of the principal groups is mechanical compression of the spinal cord or cauda equina by the encasing osseous structures and their appendages. If one excludes such of these cases as result from traumatic displacement of vertebral elements, degeneration and protrusion of the intervertebral disk, and tuberculous or neoplastic caries of the vertebrae, there then remains a group in which spinal cord compression can result from certain intrinsic osseous diseases and deformities. Of this group, the developmental abnormalities in the region of the foramen magnum and their neurologic concomitants have recently been reviewed by Spillane, Pallis, and Jones.[1] The role of cervical spondylosis in spinal cord compression has also been emphasized by the same authors[2] and by Braham and Herzberger.[3] Spinal cord symptoms are rare complications of ankylosing spondylitis, (spondylitis ankylose rhizomelique or Marie Strumpell's disease).[4] Also falling into the distinctly rare category are paraplegia due to osteitis deformans (Paget's disease)[5–7] and "kyphoscoliotic paraplegia" (paraplegia resulting from congenital or acquired kyphoscoliosis).[8–14] Similarly, there are rare examples of paraplegia resulting from achondroplasia[15,16] and hereditary deforming chondrodysplasia.[17] This list is probably incomplete. Recently it has been our experience to see two instances of paraplegia due to deformity of the vertebral column as the result of osteoporosis. A review of the Quarterly Cumulative Index Medicus and other readily available sources has led us to the belief that this role of osteoporosis had not been emphasized earlier. It is possible, however, that similar cases may have been described in other diagnostic congeries,[18–20] as will be discussed below. Accordingly, our two cases are documented herewith.

Case 1. A 72 year old white woman was admitted to the neurology service (Washington University unit) of St. Louis City Hospital on April 30, 1955. Approximately five months earlier she had developed continuous, dull aching in both ankles. Her ankles then became slightly swollen and painful on walking. These symptoms continued until the time of admission. At some ill-defined time during this interval she began to notice weakness of the lower extremities; this progressed until she became unable to walk two months before admission. During these two months, she also experienced pain in both hips. In the ten days immediately preceding admission, swelling of the right lower extremity increased considerably and involuntary jerking movements of the lower extremities appeared. There was no history of previous serious illness; the menopause purportedly had occurred at age 35.

On examination she was found to be well developed and well nourished. She was able to sit with difficulty, preferred to recline, and complained of pain in the hips. Vital signs were normal; the thyroid was diffusely enlarged. Her heart was moderately enlarged to the left and there was a grade two blowing systolic murmur at the apex. The anteroposterior diameter of the chest was increased and a few rales were heard at the lung bases. There was a prominent dorsal kyphoscoliosis, most marked in the lower thoracic spine. The uterus was three to four times enlarged and stony hard; a smaller mass of similar consistency was palpated in the left adnexa. There were hard inguinal lymph nodes on both sides. The entire right lower extremity was edematous; there was slight pitting edema over the left ankle. The bladder was distended by urinary retention. There was overflow incontinence of urine and incontinence of bowel. There were intermittent involuntary flexion reflexes of the lower extremities occurring independently on either side. These movements could be elicited readily by cutaneous stimuli. Voluntary movements of the lower extremities were weak and limited to hip rotation, toe movements, and some flexion and extension at the ankles. Deep tendon reflexes were moderately hyperactive in all extremities and equal on the two sides. Muscle strength and motor coordination were good in the upper extremities. There were

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bilateral extensor plantar reflexes. Abdominal musculature showed symmetric weakness. There was a sensory level to pain and touch at T_7 on the left and somewhat lower on the right. Vibratory perception was absent in the lower extremities.

Laboratory examinations on admission showed a hematocrit of 44 per cent, hemoglobin of 11.3 gm. per cent, 3.95 million red cell count, and a white cell count of 11,700 per cmm. with a normal differential. Urinary specific gravity was 1.010, with 2 plus albumin and 200 to 300 white cells per high-powered field. Blood urea nitrogen was 10 mg. per cent, bicarbonate 28.8, chlorides 107, sodium 146, and potassium 3.2 mEq. per liter. Serum calcium was 5.2 mEq. per liter on each of two occasions. Serum phosphorus at two determinations was 1.8 and 2.2 mg. per cent. Serum proteins were 2.6 gm. per cent albumin and 2.4 gm. per cent of globulin. Alkaline phosphatase was 2.2 and acid phosphatase 0.1 King-Armstrong units. Vital capacity was 83 per cent of normal. Venous pressure was 90 mm. of water; total circulation time was 12 seconds.

Roentgenographic examinations showed osteoporosis of the pelvis and comminuted fractures of the pubic rami on both sides. In the vertebral column there were marked osteoporosis and collapse of the bodies of T_6 through T_9 (figure 1). This produced a kyphoscoliotic deformity with the kyphosis in the mid- and lower dorsal spine and the main scoliosis in the lumbar region with the principal convexity to the right. The kyphotic deformity traversed an angle of approximately 45 degrees. In the pelvis there was a large calcified mass measuring approximately 9 cm. in its greatest dimension. A similar calcification measuring 3 cm. in diameter was located just to the left of the larger mass.

A lumbar puncture was performed at the L_4-L_5 interspace and, although fluid could be aspirated, it did not rise in the manometer. Cuff manometrics showed no rise on application of 20 or 40 mm. of mercury pressure to the neck; on application of 60 mm. pressure, the cerebrospinal fluid pressure rose to 200 mm. of water. Following rapid release, cerebrospinal fluid pressure fell slowly to 80 mm. at the end of two minutes. The fluid showed no pleocytosis; it contained 240 mg. per cent of protein and 85 mg. per cent of sugar. Cerebrospinal fluid Wassermann and colloidal gold curve were negative.

Diagnoses at this time were: osteoporosis with pathologic compression fractures of the bodies of T_6 through T_9 and pathologic fractures of the pelvis; compression of the spinal cord secondary to the vertebral lesions, with partial subarachnoid block and paraplegia; nontoxic colloid goiter; arteriosclerotic heart disease with cardiomegaly; pulmonary emphysema; calcified uterine myomata; thrombophlebitis in the lower extremities; and urinary retention with cystitis.

The patient was seen in neurosurgical and orthopedic consultations, and it was the opinion of both consultants that laminectomy would be of little value at this stage and might well make the condition worse. Upon recommendation of the neurosurgical consultant, the patient was placed on a Foster frame in an attempt to reduce the degree of spinal deformity. The frame angle was reduced gradually by taking one turn on the turnbuckle each week. The patient was also given methyl testosterone, stilbestrol, and calcium lactate orally. Stilbestrol was discontinued two weeks later because of vaginal bleeding. Bladder function was maintained with tidal irrigator, but Gram-negative bacilli were recovered from the urine on various occasions.

Deep tendon reflexes in the lower extremities became somewhat more hyperactive during the second month after admission. By the third month there was considerable diffuse muscular wasting in the lower extremities. The swelling in the lower extremities subsided gradually during this interval, and the cystitis was brought under control by tidal drainage and antibiotics. Reexamination of the vertebral column by roentgenography in the fourth month showed some decrease in the angle of the kyphotic deformity, but this was not marked. In this month the sensory level fell to S_1 and there was some improvement in the movements of the left foot. Cerebrospinal fluid manometrics were repeated during the second, third, and fifth months and these always showed evidence of partial subarachnoid block. The protein content of the fluid in the fifth month was 204 mg. per cent.

Her skin condition remained excellent throughout the hospitalization. Serum protein rose gradually to the vicinity of 6 gm. per cent, with albumin of 4 gm. and globulin of 1.8 gm. per cent in the latter part of her hospitalization.

Intravenous pyelography during the sixth month showed a mildly dilated renal pelvis and calyceal structures on the right. In the seventh month the patient's general condition had improved sufficiently that she was fitted with a back brace. With the brace she was able to sit erect for short intervals each day; these intervals were gradually lengthened. At this time a cystometrogram showed a bladder capacity of 510 cc. and a residual volume of 50 cc. The pressure-volume curve was indicative of a spinal reflex bladder; the patient was able to void reflexly and use of the catheter was discontinued. She was able to return home as a wheelchair case 11 months after admission.

Case 2. A 67 year old white woman was admitted to the medical service (St. Louis University unit) of St. Louis City Hospital on August 30, 1956. There was a 20-year history of alcoholism; her food intake had been inadequate for many years. Approximately 12 months before admission she first developed a fairly steady aching pain in the upper thoracic part of the spine. This pain persisted and became more severe about two months before admission. Pain was most

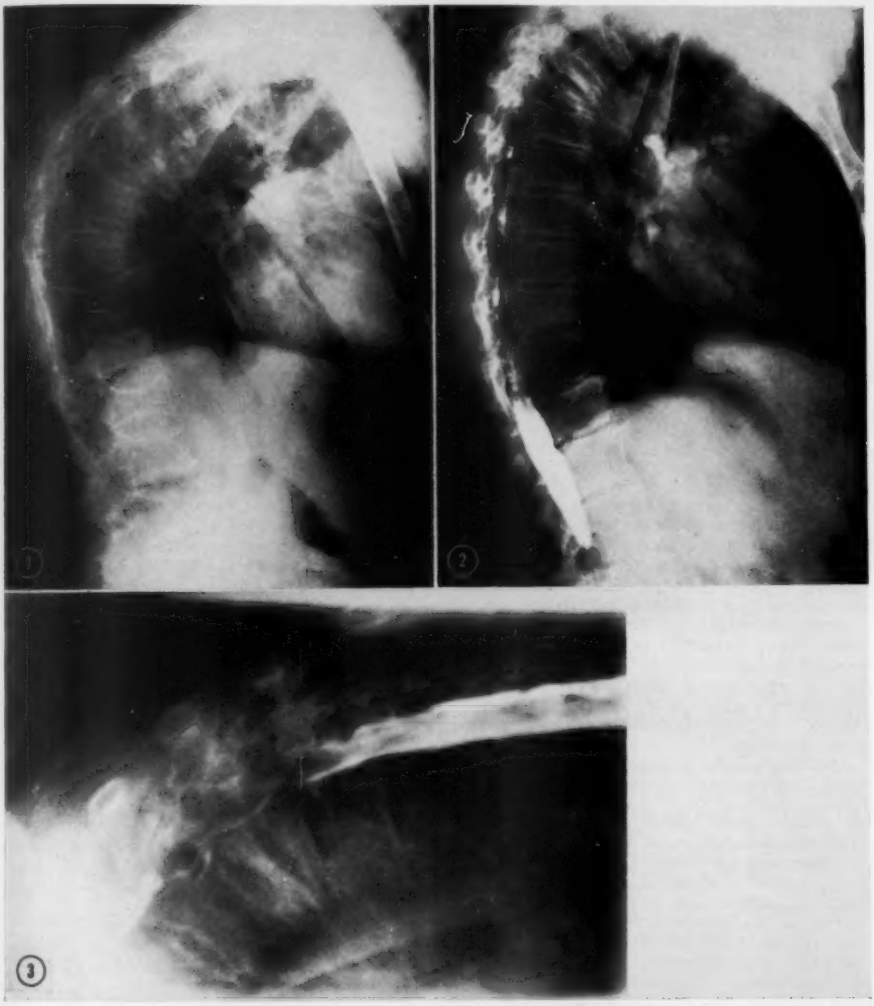

FIG. 1. Roentgenogram, *case 1*, showing extensive osteoporosis of the thoracic spine, with compression fractures of the bodies of T_6 through T_9 and the kyphosis resulting.

FIG. 2. Roentgenogram, *case 2*, showing osteoporosis of the dorsal spine, with compression fractures of the bodies of T_5 and T_6 and the kyphosis resulting.

FIG. 3. *Case 2*. Lateral view of thoracic myelogram, showing partial obstruction to flow of contrast medium, located adjacent to the collapsed bodies of the 5th and 6th thoracic vertebrae. Some Pantopaque has passed the obstruction and is seen adjacent to T_3 and T_4.

severe when she assumed the supine position and this progressed until reclining in this manner was impossible. Similarly, rotation of the spine became impossible because of intensification of pain. During several weeks preceding admission, there developed progressive weakness of the lower extremities. This proceeded most rapidly during the last week and she became incontinent of bowel and bladder. There was no history of previous serious illness, although there was vague complaint

of evanescent pains in the hips and knees for many years. The patient maintained that menstrual periods did not cease until age 60.

On examination she was poorly nourished and appeared chronically ill and older than her purported age. She was apprehensive and complained bitterly of pain; there was no deviation of vital signs from normal. Memory for recent events was poor. There was a prominent dorsal kyphosis, with paraspinal tenderness in the region from T_5 to T_8. Both lower extremities were diffusely weak but she was able to walk with difficulty. Deep tendon reflexes were hyperactive in the lower extremities and there was ankle clonus on the left. Plantar reflexes were flexor on the right and extensor on the left. There was no sensory loss in the lower extremities. The rectal sphincter was tense to digital examination.

Laboratory examinations on admission showed a hematocrit of 31 per cent, hemoglobin of 11.0 gm. per cent, 3.8 million red cell count, and a white cell count of 8,410 per cu.mm. with a normal differential. Erythrocyte sedimention rate was 40 mm. per hour; bleeding time one minute; clotting time four minutes. Urinalysis showed only a few white cells but grew *E. coli* on culture. Serum alkaline phosphatase was 4.1 King-Armstrong units; calcium, two determinations, 5.2 and 5.4 mEq. per liter; phosphorus, two determinations, 2.7 and 2.5 mg. per cent. Serum proteins were 4.0 gm. per cent of albumin and 3.5 mg. per cent of globulin. Total bilirubin was 0.2 mg. per cent. Urine test for Bence-Jones protein was negative on three occasions and a Sulkowitch test was negative on one occasion. Bone marrow examination was within normal limits. Fasting blood sugar was 87 mg. per cent and blood urea nitrogen 9 mg. per cent.

Roentgenographic examinations showed enlargement of the transverse diameter of the heart and normal upper and lower gastrointestinal series. In the thoracic spine there was compression fracture deformity of the bodies of T_5 and T_6, with nearly complete loss of the body T_5 and marked anterior wedging of the body of T_6 (figure 2). Osteoporosis of the other thoracic vertebrae was present, and it was the opinion of the radiologist that the fractures could be due to osteoporosis, although metastatic tumor was considered possible. The skull was normal radiographically.

On lumbar puncture the initial cerebrospinal fluid pressure was 60 mm. of water. There was a brisk rise and fall of pressure with Valsalva's maneuver but there was no rise with manual jugular compression. The fluid contained 27 mononuclear cells per cu.mm. and 120 mg. per cent of protein. Spinal fluid Wassermann reaction was negative.

There was a gradual increase of weakness and spasticity of the lower extremities and the right plantar reflex became an extensor response. Cystoscopy showed chronic cystitis. On October 23 the patient was seen in neurologic consultation and transferred to the neurology service. Examination at this time showed a sensory level with hypesthesia to cutaneous stimuli below the T_7 dermatome level. The patient was still able to walk by supporting herself with her hands. Shortly after this a myelogram was performed which showed a partial obstruction to the flow of Pantopaque adjacent to the collapsed bodies of T_5 and T_6 (figure 3). The lumen of the canal was narrowed by encroachment from both anterior and posterior aspects and the width of the canal was not greater than 3 mm. throughout a segment 3.5 cm. long. Shortly after this a laminectomy was performed to decompress the spinal cord. Bone fragments removed at that time showed no evidence of tumor and no tumor was found on exploration of the cord and its coverings.

Postoperatively the patient had somewhat less pain in the back, but the neurologic deficit progressed until she became unable to walk. Her lower extremities flexed spontaneously and she was put in bilateral Buck's traction on a Foster frame. Her pain was persistent, however, and she freed herself from the traction repeatedly. Because of this the traction was discontinued, although numerous attempts were made to continue it with the aid of analgesic, narcotic, and tranquilizing drugs. She was treated for pain with Demerol, codeine, Tolserol, and meprobamate, and for osteoporosis with testosterone and stilbestrol. During five months of hospitalization her total red blood cell count rose from 3.8 million on admission to 4.1, then to 5.2 million in the last month. Red cell indices were normal at the time of admission. *E. coli* was cultured from the urine on several occasions, and the patient was treated with Gantrisin and intermittent catheter drainage of the bladder. She was transferred to the St. Louis Chronic Hospital on January 10, 1957. Visited at Chronic Hospital in April 1957, she was found to have severe paraplegia-in-flexion.

DISCUSSION

A distinction between senile osteroporosis and postmenopausal osteoporosis has been made by Albright and co-workers,[21–23] and the term "postmenopausal" was substituted for "idiopathic" when the cause of this disorder was demonstrated.[21] It was admitted, however, that in many instances, osteoporosis of disuse, malnutrition, postmenopausal state, and of senility are inseparably superimposed.[23] In case 1 the unusually early age of menopause and the long subsequent period of postmenopausal life (37 years) would seem to justify the conclusion that this factor played a dominant role in the evolution of her disease. The severity of this patient's osteoporosis might thus be considered to be the result of its long period of development. It then becomes possible to understand this rare occurrence of paraplegia

as a complication of a disease so frequently encountered as to have been regarded by Albright and Reifenstein as "the commonest of all systemic osteopathies."[23]

Case 2 differs notably from the first case in two respects. Although the second patient was postmenopausal and, therefore, this state may be assumed to have influenced the development of her disease, a long postmenopausal period did not occur. Senility as a causative factor probably obtained in both cases, as may be judged from the patients' ages; the status of "senile osteoporosis" has been maintained apart from the postmenopausal factor.[23] More outstanding in case 2 is the dietary aspect; the role of protein-deficient diet in the pathogenesis of osteoporosis is an accepted one,[22,23] although the possible role of calcium- and phosphorus-deficient diets[24] seems less firmly established. The second outstanding difference between these two cases is the more restricted distribution of fractures in the second example. Although no history of trauma was obtained in this patient, the possibility of trauma must be entertained in view of the restricted site of fractures. Minor traumata are to be expected in alcoholic patients and, as is well known from the experience with subdural hematoma, this bit of clinical history is frequently wanting in such cases. It seems probable that some forgotten trauma may have occurred in this patient. A generation ago the second case might well have been diagnosed as an example of Kümmell's disease, as it was accepted that the history of a trauma responsible was not always obtainable.[20] The chimera of this supposed traumatic or posttraumatic spondylitis seems to have been dispelled by O'Brien,[20] and it is notable that one finds little reference to this presumed entity today. This view of the nonexistence of Kümmell's disease is largely supported by Key and Conwell.[25] If one assumes that a traumatic incident did occur in case 2, the least role that could be assigned to osteoporosis would be that of a strongly contributory factor, as is assumed in the case of fractures of the femoral neck.[22] It is likely that earlier lack of recognition of a relationship between osteoporosis and spinal cord compression may have resulted from an obfuscating role played by "Kümmell's disease."

Administration of testosterone and estrogenic hormone serves a dual purpose in such patients. The beneficial effect of this combination of agents in producing a positive nitrogen, calcium, and phosphorus balance in patients suffering from osteoporosis is firmly established.[23] Increased nitrogenous catabolism in acute paraplegia and its remedy by administration of testosterone has been demonstrated by Cooper, Rynearson, MacCarty, and Power.[26,27] The rise of serum protein and hemoglobin and the excellent skin condition in these patients may be attributed to this therapy. Patient 1 was under observation long enough for us to state, on the basis of clinical evidence, that the osseous disease process was arrested, at least temporarily.

SUMMARY

The literature regarding intrinsic osseous diseases and deformities which may cause spinal cord compression is reviewed briefly and the paucity of earlier reference to this role of osteoporosis is noted. Two cases of paraplegia due to osteoporosis with vertebral fractures and kyphosis are reported. The cause of osteoporosis in one was considered to be principally the postmenopausal state. In the second case, prolonged dietary inadequacy seemed most significant, although unrecognized trauma may have been a factor in causing the fractures. Testosterone and estrogenic hormone serve a dual therapeutic purpose in such cases, both in the augmentation of nitrogen, calcium, and phosphorus metabolism in osteoporosis and for the reversal of the accelerated nitrogenous catabolism which occurs with acute paraplegia.

We are indebted to Dr. Louis L. Tureen for permission to report case 2.

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■ I will make a few remarks on the treatment of epilepsy proper. For the negative functional state in hemiplegia we can do nothing; nervous elements are in most cases gone, and in postepileptiform hemiplegia the paralysis needs no treatment. In epilepsy the other, the diametrically opposite, kind of functional state is a very different thing in its therapeutical bearings. It is notorious that our treatment of epilepsy is deplorably unsatisfactory, and if my hypothesis be correct — that there is a persisting local lesion in the highest centres of one side of the brain — there are good reasons for it. The radical cure of epilepsy, as of epileptiform seizures, is for the surgeon to cut out the "discharging lesion"; but in no case of epilepsy proper do we as yet know its exact position; it will differ in different epilepsies. Still we may interfere for good in the local over-active process of nutrition, always going on, which keeps up the high instability of cells of the "discharging lesion."

J. Hughlings Jackson in *Remarks on the Diagnosis and Treatment of Diseases of the Brain*, published in 1888.

Some where's and why's of neuritis

A consideration of structures and causes

Henry W. Woltman, M.D. and Norman P. Goldstein, M.D.

AMONG ILLNESSES, as among people, there are artful dodgers. They may appear anywhere, but commonly they consort with evil associates. Neuritis is one of these dodgers and, whatever the dodge, the illness is the concern of those who practice medicine. It has been said that neurology is the queen discipline of medicine. Some may challenge this, but neurology is a fabric of two basic sciences, anatomy and physiology, and they are applied in finding answers to two basic questions: Where is the lesion? Why is the lesion? The two sciences, then, are the bow and the bit of the master-key that unlocks the diagnosis. Therefore, it will be helpful, first, to view neuritis as a whole in relation to the where and the why, and then carefully to inspect some of its manifestations in the form of identifiable diseases, to which names have been given.

RELATION OF ANATOMY AND PHYSIOLOGY TO THE WHERE AND THE WHY

A unique feature of the nerve cell is its extraordinary length. In its course, the long bundle that nerve cells form may lie next to skin or bone; it may pass through muscles, ligaments, and foramina or tunnels; proximally, the roots of a spinal nerve lie in relation to structures of the spinal column and, distally, its fibers diminish in caliber and lose their myelin sheaths. All of these anatomic vicissitudes represent hazards and the places where the hazards are encountered are common sites of injury.

Besides length, it is helpful to recall certain other anatomic features of nerves. Every physician knows these features, yet he may disregard them habitually unless he has schooled himself to include them in his thinking. Microscopic examination of a nerve discloses nerve fibers, blood vessels, and connective tissue. Each fiber has a central core of viscid axoplasm, the axon, which is essential to conduction of a nerve impulse. The axon is encircled by a myelin-laden sheath of Schwann cells; this sheath is important in facilitating the impulse and setting its speed. Both axons and sheath cells are sites of elaborate enzymatic systems that can be blocked by toxins. Nerve fibers differ in diameter, in degree of medullation, and in function. Consequently, they differ in susceptibility to injury of various kinds and this may explain the varying symptoms of neuritis.

As we have suggested, even a physician may forget that nerves have blood vessels and connective tissue. But nerves are richly supplied with blood vessels and, if disease of them results in ischemia, effects may be devastating. Nerve fibers also are provided with a safe housing of connective tissue. This may become infected, scarred, edematous, hypertrophied, or invaded by neoplasms and, thus, may cause secondary injury to nerve fibers.

In general, but only in general, it may be said that when neuritis affects one nerve (mononeuritis), adjacent nerves, or a plexus of nerves, the cause commonly is a mechanical one; that when several, single major nerves are affected simultaneously, a situation that may be described as mononeuritis multiplex, the cause is often a vascular or allergic one; and that when nerves are affected diffusely, as in the disorder known as multiple neuritis, the cause is often a toxic, viral, metabolic, or allergic one, rarely an hereditary one. Finally, it is well to note that various causes of neuritis, as is true of so many debts, are cumulative.

RELATION OF THE HISTORY TO THE WHERE AND THE WHY

In the diagnosis of neurologic diseases, including neuritis, the patient's history is usually the most important contribution. Therefore, it behooves the physician not to lean too heavily on words a patient may use to describe a stubbornly obtrusive condition of which he is afraid. Words should be scrutinized for the meaning the patient intends to convey. For example, a patient may say his face is *stiff* or *numb*, but he may mean neither.

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Read before the Canadian Medical Association, Edmonton, Alberta, Canada, June 21, 1957.

Because the word neuritis implies a structural misadventure of a nerve, the numbness that the condition may cause cannot be rubbed away. Sedulous inquiry into occupation and habits is also rewarding. We shall not belabor this matter of taking the history beyond adding Richard Bright's remark that the most useful instrument the physician carries is a blue skin-pencil. Bright wished to know where, exactly where, is the patient's discomfort and exactly where his disorder is evident on examination.

RELATION OF THE EXAMINATION TO THE WHERE AND THE WHY

Before a diagnosis of neuritis is assured, objective confirmation of sensory, motor, or autonomic impairment consistent with the distribution of the nerve supply should be sought. As in taking the history, so in making the examination, pitfalls may be encountered; of them we shall mention a few that appear to be most troublesome. Testing of sensation is always tedious. Insistence on prompt replies when stimuli are applied not only saves time but eliminates opportunity for deliberation, a trait of some patients that conduces to the development of hysterical or factitial anesthesia. Such a development only makes solution of a hard problem harder. A word of disapprobation or one of praise also helps wash away hysterical anesthesia.

The examiner will be cognizant of adherent or cut tendons, stiff joints, and so-called reflex atrophy of muscles near diseased joints, and he will beware of trick movements made by substituted muscles. Most of these cause no trouble if muscles or tendons are palpated when the command is given to make one specific movement once and no other movement. It is well to bear in mind that a small movement may be a strong movement and, as far as function of the nerve is concerned, a satisfactory one.

We need a special compartment to remind us of an obvious thing to do, namely, to palpate the nerves with care. Attributed to Calvin Coolidge is the aphoristic comment, "The last thing a deep sea fish discovers is salt water."

The physician also will be alert to the hallmarks of neurotic behavior. Rather early in the course of taking the history, he may note some resentment or irrelevance on the part of the patient when precise answers are sought. Other suggestions of functional disorder are 1) dramatic display of ineffectual effort; 2) inability to move a member but great ability to resist its passive movement; 3) a plastic, leaden giving way when stress is applied, followed by absence of elastic comeback when stress is released, and 4) incongruous sensory deficits.

Of decisive help in diagnosis and prognosis is electromyography. The decision rendered is usually final. However, performance of the examination and interpretation of sounds and tracings lie within the province of the neurophysiologist, for these require great experience as well as clinical interest.

And now let us turn to some often encountered neuritic disorders to which names have been given.

EXAMPLES OF MONONEURITIS AND OF INVOLVEMENT OF PLEXUSES

The facial nerve. Paralysis in the region of distribution of the seventh cranial nerve, or Bell's palsy, usually includes muscles supplied by all branches of the nerve. Causes are many, but in about 68 per cent of cases, the palsy is of the so-called rheumatic type and often follows exposure to a cold draft; the left-sitting driver of a motor car has it on the left side, his passenger, on the right. Onset is usually measured in terms of hours. An onset taking weeks or months, noted in about 4 per cent of cases, suggests the possibility of tumor. Little more than the nerve and its attendant blood vessels can be accommodated in the facial canal and it is here that the nerve usually is injured. Since the chorda tympani accompanies the seventh nerve for a short distance, taste often is lost over the anterior two-thirds of the tongue. If the lesion is higher still, the stapedius muscle may be paralyzed, with seeming change in pitch or increase in loudness of sound. Damage may be so slight as to blockade only the passage of the impulse, and, in this event, recovery may follow within a week or two. However, if continuity of the axon has been interrupted, the nerve must undergo regeneration before recovery will take place. Nerves grow like children – only so fast – and return of function in the part of the face supplied by the seventh nerve usually is not even hinted at in less than six weeks.

The facial nerve illustrates more clearly than any other, with the possible exception of the oculomotor nerve, what happens during regeneration. As a result, the physician can almost always recognize old facial palsy, whether the patient can or cannot confirm that he had it. When nerves regenerate, their growing axons, which also sprout additional branches, lose their way and many arrive at

a wrong destination. To this may be added the possibility, under certain conditions, that a passing impulse may start one in an adjacent fiber. Consequently, some impulses intended for the eyelids find their way to the lips, causing lids and lips to move synchronously; or, while the patient is eating, impulses may arrive at the lachrymal gland and cause tears to flow, the so-called syndrome of crocodile tears.

The ulnar nerve. One of the most commonly afflicted of all nerves is the ulnar. Loss of its motor function is of greater consequence than is loss of its sensory function.

If one were to guess where this nerve might be hurt most often, he would think of the elbow where the nerve rides in its groove and lies immediately under the skin. One's chances of being correct would be about 67 per cent. A common feature of lesions in this situation is slow progression. An elbow may be fractured at the age of seven years but palsy may not begin until the age of 40; such a condition often is referred to as tardy ulnar palsy. In the presence of arthritis of the elbows the nerves of both arms may become affected, which sometimes leads to an erroneous diagnosis of amyotrophic lateral sclerosis. Usually an arthritic elbow cannot be straightened completely; the nerve is tender, indurated, enlarged, and, on flexion of the elbow, may slip over the internal condyle of the humerus, each time adding a little to the injury. Palsy also may appear if the nerve is compressed between bones of the elbow and the bedding or the arm of a chair. A surgical operation peculiar to the ulnar nerve is transference from its groove to the anterior aspect of the elbow.

The ulnar nerve again becomes superficial at the wrist. In 14 per cent of cases of one series it was lacerated or received occupational injury here.

The median nerve. Especially intolerant of injury is the median nerve. This nerve carries unusually large complements of sensory and vasomotor fibers that are of greater importance to function of the hand than are the motor fibers. Perhaps also because of these qualities of function, the diagnosis may be missed. An example may be cited:

Case 1. In 1917 a female nurse 18 years of age complained of aching pain and paresthesia in both arms, forearms, and hands, with the possible exception of the little fingers. The difficulty was especially troublesome at night, when the patient could sleep only if sitting up, the hands supporting the elbows and pushing the shoulders upward and forward. Assumption of this position stopped pain and paresthesia "like turning off a light."

In 1940 a supraclavicular thrill was heard and, since the pain had become worse, bilateral scalenotomy was performed. The operation did not confer relief of pain. In 1942 roentgenologic examination of the wrists gave negative results. In 1946 the patient demonstrated, as she had done every time we had seen her, how she slept: hands under elbows, shoulders up and forward. A costoclavicular syndrome was considered and part of the right first rib was resected. This did not help.

In 1949 slight weakness and atrophy, localized to the right abductor pollicis brevis, was observed. Since the right side was the more painful of the two, the right anterior transverse carpal ligament was sectioned, although with misgiving. The following morning the patient reported that the right arm and hand were well. But it was decided to see whether the improvement would be permanent. It was. In 1950 the left ligament was sectioned also.

In 1952, when the woman was 53 years of age, she reported that she had been free of pain since these operations. And, at last, we who had had care of her realized that we had observed the position of her shoulders but not that of her hands as she demonstrated how she had sat through the nights. In this position the wrists had been extended. We learned also that the whole extremity may hurt in median neuritis, even though the lesion is at the wrist.

Such delay in making a diagnosis of the carpal tunnel syndrome is no longer necessary, since compression of the nerve at this site can be demonstrated by electromyography.[1] Thus, if it takes 8 milliseconds for an impulse applied at the wrist to reach the muscles supplied by the median nerve instead of the normal 4.8 milliseconds or less, the finding is significant, even though denervation of muscles may not be demonstrable. We must not leave you with the impression, however, that there are no other causes of median neuritis. There are many, but this is the most common.

The radial nerve. The most important function of the radial nerve is motor, and paralysis of muscles in its distribution may leave the hand almost useless. This nerve, like the ulnar, is most vulnerable where it is most superficial. Compression of the nerve at its humoral sulcus has given rise to such appellations as coachdriver's paralysis, Saturday night paralysis, and bridegroom's paralysis; but in the case you saw last it probably followed a visit to the movies during which the arm found its way between adjoining seats.

Although sensory function of the radial nerve is almost negligible, its distal cutaneous ramus may be compressed by the band of a

wrist watch. The resulting minor affliction has been given the imposing appellation cheiralgia paraesthetica, which people commonly call a pain in the hand.

Another branch of the radial nerve should not be slighted. It is the entirely motor dorsal interosseus nerve. Following is a case in point:

Case 2. A girl 13 years of age complained each time she sat down at the piano to practice that she could not raise one of the fingers of her right hand. Meanwhile all extensor muscles supplied by the posterior interosseus nerve had become paralyzed, one at a time. At the age of 37 years, a lipoma that compressed the upper part of this nerve was removed.

In such cases it is advisable to request that roentgenograms be taken in such a way as to represent soft tissue, since a lipoma in the region concerned imparts to the palpating hand only the vaguest suggestion of a mass.

The course of the radial nerve makes it difficult to approximate severed ends. Fortunately, results of tendon transplantation are often superior to those obtained by suture of the nerve.

The brachial plexus. For most practical purposes, it might be said that the brachial plexus begins with five nerves and ends with five principal nerves.

Although deeply situated, the position of the brachial plexus is not a safe one. By far the most common cause of brachial neuritis is trauma. This was a factor in at least half of 400 cases that were reviewed. Among the most serious kinds of trauma are avulsions, or tears, usually from above downward. The plexus may also be injured by fractures, dislocations of the shoulder, and compression by crutches. The autogenetic compression-traction syndromes, often referred to as outlet syndromes, involve more subtle applications of stress to the plexus.

Tumors involved the brachial plexus in 20 per cent of the 400 cases analyzed. Of these tumors, the greatest number consisted of extensions from carcinomas of the breast, sometimes years after mastectomy. Others may come from the lung. When paralysis, anesthesia, edema, and pain sufficient to cause sleepless nights progress ominously from week to week, malignant invasion should be considered.

Radiculitis. Often the cause of neuritis is in or near the spinal column. This possibility is suggested when pain, weakness, and sensory loss are segmental in distribution – and this is when Richard Bright's blue skin-pencil is especially helpful – when coughing or movement of the head accentuates the pain, or when vertical traction on the head relieves discomfort. Common causes of radiculitis are trauma, protruded intervertebral disk, arthritis, and tumor. Muscles located near the spinal column cannot be tested easily by usual methods of examination but electromyography often gives decisive information.

The external peroneal nerve. A man who has sat with legs crossed at a prolonged, absorbing baseball game, wake, or poker party may discover that he has lost the power to dorsiflex his foot, the left one more often than the right. Many patients are unaware that, in addition to foot-drop, sensation over the dorsum of the foot and anterolateral aspect of the leg may be impaired. Crossed-leg palsy is caused by compression and ischemia of a segment of the common peroneal nerve as it lies wedged between the head of the fibula and the opposite knee. The ankle jerk is, of course, preserved. The disability is bilateral in 18 per cent of cases and is at least four times as common among men as among women.

Sitting tailor-fashion or squatting may compress the nerve between the head of the fibula and the tendon of the biceps femoris. Hence, this type of occupational neuritis has been named oyster sorter's paralysis and gardener's paralysis.

Not to be confused with crossed-leg palsy is the foot-drop of the anterior compartment syndrome. This is caused by ischemia of precariously nourished muscles that are encased in the anterior compartment of the leg. A long march may precipitate this serious but fortunately uncommon circulatory event.

The lateral femoral cutaneous nerve. Earlier, when the topic was the radial nerve, a type of cutaneous neuritis called cheiralgia paraesthetica was mentioned. In the lower extremity occurs meralgia paraesthetica, meaning pain and disturbance of sensation in the thigh. This affliction of the purely sensory lateral femoral cutaneous nerve occurs three times as often among men as among women and usually among persons who are overweight. It is bilateral in 20 per cent of cases. The nerve usually is injured where it passes under the inguinal ligament or at its site of transit through the fascia lata. Local tenderness may be found at these sites.

The lumbosacral plexus. Although the lumbosacral plexus lies in a sheltered place, it does not escape violent trauma. But of greater importance were the 36 per cent of cases in a series of 77, in which the plexus was invaded

by malignant growths. In very painful unilateral femoral neuritis malignancy is the most common single cause, especially among men. On the other hand, when very painful femoral neuritis is bilateral, the first consideration is diabetes mellitus. The patient is likely to be a woman, perhaps because diabetes is more common among women than it is among men.

Case 3. In November 1955 a woman complained bitterly of pain caused by right femoral neuritis. Urinalysis, determination of blood sugar, and the glucose tolerance test gave normal values. By April 1956 the pain had ceased but the patient had, instead, severe right sciatic neuritis. When she returned in January 1957, the sciatic pain had disappeared but she had bilateral femoral neuritis. This time the value for blood sugar was increased and the glucose tolerance test was characteristic of diabetes, although routine urinalysis disclosed no glycosuria.

The outlook for recovery from this type of neuritis is good but the condition may last a long time.

MONONEURITIS MULTIPLEX

Thus far, the discussion has been concerned with involvement of single nerves (mononeuritis) or with plexuses. The environment of the nerve concerned often determines the site of the lesion. But there are conditions in which several isolated and often widely separated nerves are injured simultaneously or in rapid succession. Such a series of events may be characteristic of the condition referred to as mononeuritis multiplex. In mononeuritis multiplex, trouble usually starts within the nerve itself. An example of this is local infectious neuritis, such as occurs in leprosy.

In this category of scattered and often abruptly emerging neuritis are several varieties of allergic origin, among them serum paralysis. In serum paralysis the average interval between the first injection and the onset of serum sickness is about seven days, and between the onset of serum sickness and neurologic complications, two days. Early administration of cortisone may arrest progress of paralysis or sensory loss.

In the presence of periarteritis nodosa, the onset of neuritis often betrays the nature of an obscure cardiac, renal, gastrointestinal, or other illness from which a patient may have been suffering. Of 29 cases of periarteritis nodosa in which necropsy was performed, Lovshin[2] noted that there was a history of neuritis in about half. In about half of these, in turn, there had been evidence of mononeuritis multiplex and, in the other half, evidence of multiple peripheral neuritis. The blood vessels of the nerves were badly diseased in all cases in which neuritis had developed.

In acute porphyric neuritis, muscles in the region of distribution of one or more nerves may become paralyzed within a few hours after onset of weakness. No cure is known, but administration of barbiturates or use of alcohol should always be avoided. Goldstein, Martin, Brunsting, and Kirby[3] suggested the administration of chlorpromazine hydrochloride, opiates, paraldehyde, or chloral hydrate for relief of pain. A diet high in carbohydrates and protein is recommended.

MULTIPLE PERIPHERAL NEURITIS

When bilateral, symmetric, peripheral involvement of nerves makes its appearance, some substance, process, or deficiency capable of acting diffusely should be considered in search for the cause. Among these are bacterial, chemical, and metabolic poisons, allergy, and lack of substances needed to maintain the functions of nerves. The effect is primarily on neuronal structures; the condition is a variety of polyneuropathy.

Formerly the most commonly recognized causes of polyneuritis were diphtheria, prolonged sepsis, and arsenical poisoning. Technical advances have introduced new toxins and several cases of polyneuritis caused by weed killers and insecticides have been documented.

Nowadays one of the most common forms of polyneuritis is the Guillain-Barré syndrome, or neuronitis. Its cause is not known, but the condition may be found in company with many apparently unrelated diseases. A virus has not been excluded as a possibility and there are good reasons for considering an allergic mechanism. On this basis, cortisone has been administered, apparently with favorable response in some cases.

Deficiency still is a cause of neuritis and, indeed, new causes in this category have been added. As Gammon, Burge, and King,[4] Biehl and Vilter,[5] and Hines,[6] among others, have shown, administration of isonicotinic acid hydrazide in the treatment of tuberculosis may cause severe peripheral neuritis. Apparently this neuritis is related to increased excretion and consequent deficiency of vitamin B_6 (pyridoxine), which results in altered breakdown of the amino acid, tryptophane. Such neuritis does not occur if supplementary pyridoxine is administered while the patient is under treatment with isonicotinic acid.

EPILOGUE

Nerves are comparatively simple neurologic structures, but in form and function they are impressive. Their fibers are in the neighborhood of 2 to 20 microns in diameter, but they may be a meter or a million microns in length. Depending on the diameter of the fiber, an impulse may journey the length of a fiber in one-half to one-hundredth of a second. These speeds are comparable respectively to those of a leisurely walk (three miles an hour) and of an airplane (180 miles an hour). By virtue of intraneural plexuses, fibers are continually redistributed so that, in some places, a cut half way through a nerve does not have disastrous consequences. Each impulse has its own lane and, at regular intervals, nodes control and supplement its speed and energy. Along their way, impulses may encounter sharp curves and tunnels which present hazards as similar obstacles would do on highways. Highways fall into disrepair. But in nerves such dissolution is not expected and generally, in nerves, the traffic proceeds smoothly over the span of a lifetime, which may approach, or even exceed, 100 years. Then we who know something of the nervous system pause to wonder how it all came about, and why all of us do not have neuritis all of the time. Perhaps the answer is that we are neither the architects nor the drivers.

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■ When the continuity of the cord as a conductor is entirely interrupted by being cut, torn, compressed, or injured in any other way, voluntary movement and sensation are immediately abolished in the parts behind the injury, and at the same time the paralyzed muscles, especially in the lower extremities, become much more susceptible to reflex action. The increased susceptibility to reflex action is developed immediately, or all but immediately, and it may continue with little change for days, weeks, or even months — a fact which does not appear to be very intelligible on the current view of muscular action, but a fact nevertheless. The higher the seat of injury to the cord, the higher must be the level to which the paralysis reaches, and (if the respiratory muscles be affected at all) the greater the interference with the breathing, and, as may be easily understood, it is not difficult to form a tolerably correct diagnosis of the locality of the injury by taking these variations into consideration.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

Occurrence of neurologic abnormalities in infants of diabetic mothers

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A SURVEY of the literature on the offspring of diabetic mothers indicates a higher mortality rate and a greater incidence of congenital malformations as compared with non-diabetic controls. Pedowitz and Shlevin[1] estimated the mortality rate in offspring of diabetic mothers to be as high as 8.2 per cent. According to Kade and Dietel,[2] the incidence of congenital malformations in diabetic pregnancies is 3.6 per cent (110 deliveries) as compared to 0.5 per cent in normal controls (1,000 deliveries). There are no statistical data on morbidity of the infants born to diabetic mothers. Similarly, very little information is available regarding the clinical manifestations and subsequent course of these patients. In the present communication an analysis is made of the neurologic abnormalities encountered in the offspring of diabetic mothers.

Although many authors stress the increased incidence of congenital malformations and birth injury in the offspring of diabetic mothers, there are only a few reports in which the investigators described the type of abnormality or gave the size of their sample. LeCorche[3] was probably the first to report abnormalities in children born from diabetic mothers; two of the infants described by him were born with pronounced hydrocephalus.

In a series of 17 pregnancies in diabetic patients, Peckham[4] found one infant stillborn with congenital syphilis and one child with a meningocele. Skipper[5] investigated 37 pregnancies in diabetic women and found two malformed infants; one was born a "monster" and the other had a congenital heart defect. He felt that, although there were too few cases to allow definite conclusions, there seemed to be a tendency for children of diabetics to show congenital abnormalities. White and coworkers[6] stated that congenital defects occurred in three out of 35 patients; only one was considered to have a neurologic abnormality. Gasper[7] analyzed histories of 49 pregnancies in diabetic women; one patient had three stillbirths and then delivered a "monster with many anomalies." Palmer and Barnes[8] mentioned the occurrence of a "deaf and dumb" child among those resulting from 68 pregnancies in diabetic mothers. Miller[9] surveyed 19 consecutive autopsies of infants born to diabetic mothers and found single or multiple congenital malformations in six. One of them had anencephaly, another had malformation of the spine, harelip, and syndactyly, and the remaining four had malformations of various internal organs.

Gonce[10] stated that congenital abnormalities occur in one out of six children whose mothers were diabetic, whereas they occur in only one out of 55 normal births. The incidence of involvement of the central nervous system was not given. Hall and Tillman[11] summarized the causes of fetal deaths occuring with diabetic mothers as follows: 1) spontaneous abortion, 2) hydramnios, 3) congenital abnormalities, 4) acidosis, 5) hypoglycemia, 6) toxemia, 7) prematurities, and 8) large babies. There were no congenital abnormalities in their series of 149 pregnancies in 112 diabetic patients. Kloos[12] reported that congenital abnormalities were found in three of four infants born to diabetic mothers. Two were siblings, however, and were born of a mother who herself was disproportional. Both had a congenital heart con-

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dition; in addition, the older one was microcephalic and the younger hydrocephalic. The third infant considered abnormal had a slight hydrocephalus and splenomegaly. Mengert and Laughlin[13] reported that one child in their series of 33 had an intracranial hemorrhage but no congenital anomalies were found. Sisson[14] reported one death from intracranial hemorrhage in a series of 65 infants born of diabetic mothers, but did not mention central nervous system malformations. Whitely and Adams[15] mentioned one infant who died of intracranial hemorrhage after a difficult delivery through a narrow passage. They found five congenital abnormalities in their series of 79 pregnancies complicated by diabetes. These included tetralogy of Fallot, cleft palate, imperforate anus, stricture of the rectum, and microcephaly. Keleman[16] found hemorrhages in the middle and inner ear in a 22-week human fetus delivered by cesarean section.

PRESENTATION OF CASES

Case 1. The maternal grandmother and great grandmother died of diabetes. There was no family history of other hereditary disorders or nervous disease, except for the patient's siblings who will be discussed later.

The mother developed diabetes mellitus at the age of 19, during her first pregnancy. The pregnancy was further complicated by thyrotoxicosis, which was successfully treated medically. She was maintained on insulin and had no apparent difficulty with the diabetes. Labor and delivery were normal, but an oversized female infant weighing 9 pounds and 3 ounces was stillborn. Following a thyroidectomy at age 21, she was fairly well stabilized on insulin.

At age 23 she again became pregnant and required an increase in insulin. However, she did not adhere to the prescribed diet and suffered several severe episodes of acidosis and insulin hypoglycemia throughout her pregnancy. A pelvic roentgenogram taken at the beginning of labor in the thirty-eighth gestation week disclosed twins, one of whom had a very large head. The infant with the smaller head was born first without difficulty (case 1). Respiration was established within two minutes and his general condition was satisfactory. He weighed 2 pounds and 8 ounces; his head was microcephalic and the anterior fontanel was abnormally small.

The second twin was delivered after internal podalic version. Following delivery of the body, the head would not descend. Twenty-five cc. of cerebrospinal fluid were removed by cisternal puncture in an attempt to decompress the head. By this time the fetus was dead, and delivery was accomplished by craniotomy. There was no polyhydramnios. The length of this twin was 52 cm. and he weighed 7 pounds and 3 ounces. His head was estimated as "twice the normal size." The gross and microscopic examination of the viscera showed congestion of the lungs, liver, spleen, and thymus. Examination of the brain was handicapped by damage during delivery. The lateral ventricles could be recognized and both were markedly dilated. No further identification of structures was possible.

The viable twin (case 1) developed convulsions on the fourth day which were improved after the administration of glucose. He required incubator care for the first four weeks. During the second month moderate muscular rigidity was noted. He cried frequently, took his formula poorly, and vomited often. His physical and mental development was grossly retarded. He first rolled over at the age of two years, he sat up and began to utter indistinct syllables at three years, and at four his locomotion was limited to crawling. At the age of three he had a further series of convulsions associated with a high fever.

Examination at the age of five and a half years: The patient's weight was 12.9 kg. and height 96 cm. His head circumference was 43 cm. (normal for this age is 52.3 cm.), with decreased breadth in the frontal region. An umbilical and right inguinal hernia were present. The general physical examination was otherwise normal.

He was very irritable. He had no intelligible speech except for an indistinct "hello." He could pull himself to a standing position on the crib railing but could not stand unsupported. The estimated developmental age was between ten and twelve months. The cranial nerves were normal. There was a moderate spastic weakness, greater in the lower extremities and most pronounced on the left side. The left leg was shorter and smaller than the right and there were contractures of the left knee and ankle (figure 1). When led, the patient was able to take a few awkward steps. Skilled movements were performed poorly but there was no gross cerebellar incoordination. He displayed mirror movements in his left hand while using the right. Pain perception was normal. The tendon reflexes were very brisk, especially in the left upper extremity.

General laboratory and cerebrospinal fluid examinations were normal. Urinary excretion of alpha-amino acid was 25 mg. in 24 hours. Tests for toxoplasmosis and phenylpyruvic acid were negative. An electroencephalogram showed a moderate diffuse dysrhythmia. Roentgenograms of the skull were normal, except for over-all smallness. Pneumoencephalography revealed slight ventricular dilatation, especially in the posterior portions (figure 2).

Comment: Maternal diabetes was poorly controlled throughout the pregnancy, and at birth one of the twins was hydrocephalic, the other microcephalic. Only the latter infant survived, but

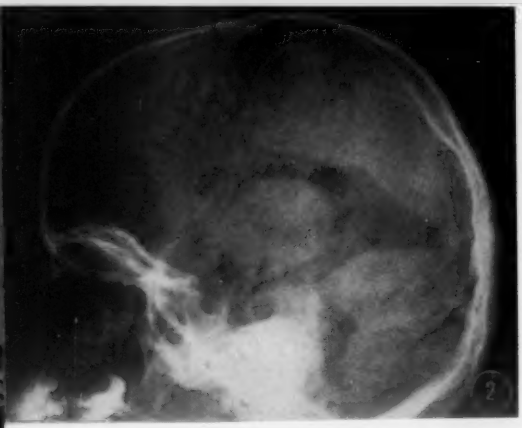

FIG. 1. *Case 1.* The patient is unable to stand without support. Smallness of the head and contracture of the left leg are apparent.

FIG. 2. *Case 1.* Pneumoencephalogram. Normal appearance of lateral, third, and fourth ventricles, except for slight enlargement.

showed spastic diplegia, mental deficiency, and microcephaly. The underlying pathologic lesion may consist of defective formation of the cortex, for example, microgyria, or neuronal damage at a later stage of development. In any case the abnormality must have developed during prenatal life in both twins, most likely after the second or third months of gestation.

Case 2. A four year old brother of case 1. Throughout this pregnancy the mother, then aged 24 years, was still under very poor diabetic control. She had several episodes of acidosis and was in coma twice during the second and third trimesters. Numerous hypoglycemic reactions occurred throughout gestation. Diabetes was brought under control at the end of the eighth month and the infant was delivered by cesarean section, weighing 7 pounds and 8 ounces and having a small, narrow head.

Respirations were not established for the first few minutes after birth. Subsequently the patient had several convulsions, became cyanotic, and had to be placed in an incubator. His blood sugar was 32 mg. per 100 cc. and glucose was given orally and parenterally. At birth it was noted that his head was small and narrow. His general condition at the age of two weeks was good and his blood sugar was 102 mg. per 100 cc. His subsequent general development was markedly retarded. He began to roll over at 14 months and sat up without support at 30 months. At three years he vocalized indistinct syllables and was creeping around the room.

Examination at the age of four years: The patient's weight was 12.8 kg., height 96.5 cm., head circumference 49.0 cm. (normal 52.1 cm.). General physical examination was normal. Mental development was grossly retarded and corresponded to about the age of 11 months. He could stand only if supported, his usual locomotion being creeping or "walking" on his knees. His speech consisted of unintelligible sounds and he showed no understanding of simple commands.

The cranial nerves were normal, except for slight bilateral esotropia and moderate slowness in facial movements. Like his brother, he had spastic diplegia, the lower extremities and the left side being more affected (figure 3). He had a slight contracture of the left knee and an equinovarus deformity of the left foot. Sensory examination was normal. Although his movements were performed with poor motor skill, no gross cerebellar incoordination was present. The tendon reflexes were very brisk, moreso on the left. The left plantar response was extensor, the right equivocal.

General laboratory and cerebrospinal fluid examinations were normal. The alpha-amino nitrogen excretion in the urine was 50 mg. in 24 hours. Tests for toxoplasmosis and phenylpyruvic acid were negative. An electroencephalogram revealed diffuse irregular sharp and diphasic waves arising from both hemispheres. Roentgenograms of the skull were normal except for smallness. Pneumoencephalograms demonstrated slight dilatation of the entire ventricular system without significant asymmetry (figures 4 and 5).

Comment: The control of maternal diabetes was even worse than during her preceding pregnancy. She suffered acidosis, coma, and many hypoglycemic reactions. The infant's development was grossly retarded and he had spastic diplegia. The presence of microcephaly at birth suggests that the brain abnormality occurred during prenatal life. The pathologic changes in the brain may consist of cortical dysgenesis or neuronal damage. The cyanosis and convulsions after delivery can be also more easily explained by assuming that his central nervous system was already defective prior to birth.

Case 3. There was no family history of nervous or mental illness, but a strong history of diabetes was present on the maternal side. The patient's maternal grandfather was diabetic and both the maternal great-grandmother and grandmother died of diabetes mellitus. The mother developed diabetes two years prior to the birth of this patient. The patient has one normal sibling, a brother two years older, and several years after the patient was born the mother gave birth to a ten pound stillborn infant.

The patient's mother developed glycosuria at the age of 25 when pregnant with her first child. The glycosuria cleared after a few months and an eight pound infant was born without difficulty. His subsequent development was normal. The mother's subsequent diabetic management had been irregular and inadequate due to fear of insulin injections. The mother had glycosuria throughout the pregnancy, but made no serious attempt to control it. She felt tired and slept excessively but there was no coma. Labor began at full term in the R.O.P. position; after 16 hours a midforceps delivery was accomplished without difficulty. Respirations began promptly and the infant, who weighed 11 pounds and 11 ounces, was in good condition. On the fifth hospital day, he was discharged in satisfactory condition.

During the first few months of life the infant was unusually quiet, but ate well. Subsequent development was retarded. He first sat unsupported at one year and walked with one hand held at 16 months. At three years, when he was able to utter only a few indistinct words, his mood changed from complacency to hyperactivity and destructiveness. His intelligence quotient at age five was 32 on Stanford Binet and 44 on the Merrill-Palmer scale.

Examination at the age of eight years: The patient was a well developed and well nourished boy. The general physical examination was normal. The head was well formed, symmetric, and normal in size. He was very restless and had a short attention span. His speech consisted of single words and only occasionally did he join two or three words together. He was incontinent.

The cranial nerves were normal, except for slight bilateral esotropia. Motor ability was fairly good; he could walk up and down stairs. Skilled movements of hands were slightly awkward. Pain perception was normal. There was no evidence of cerebellar incoordination. The tendon reflexes were brisk and equal and plantar responses were flexor.

General laboratory examinations were normal, including tests for toxoplasmosis and phenylpyruvic acid. An electroencephalogram showed moderate diffuse dysrhythmia, with irregular fast activity but no focal abnormality. Roentgenograms of the chest, skeleton, spine, and skull were normal.

Comment: The mother had only moderate diabetes but it was porly controlled. The infant was oversized and had to be delivered by midforceps because of face presentation. His condition immediately after birth was good. However, subsequent development was retarded in all spheres. At the age of nine years his intelligence quotient was below 45, but his motor performance was satisfactory and there were no focal neurologic signs. It is difficult to ascertain the underlying cerebral pathology in this patient. However, slight awkwardness of skilled movements and a marked degree of mental deficiency suggest diffuse abnormality on the neuronal level. Although it cannot be entirely excluded, cerebral birth injury is unlikely, as his condition during and after delivery was normal. Conceivably, a disturbance affecting neurons at a late stage of gestation can be implicated.

Case 4. The mother, now 65 years of age, developed diabetes at the age of 30. Despite insulin and diet, most of her blood sugar estimations were abnormally high, but she gave no history of coma. Of her 17 pregnancies, eight children are living; of the remaining nine, three were stillbirths. Four of the living children are of average intelligence, two are mentally dull but able to earn their living, and the other two (the patient and his fraternal twin) are mentally defective and emotionally disturbed, respectively.

The patient and his twin brother were born three weeks prematurely. The mother's diabetes was difficult to control but no episodes of coma are known. At birth the patient was the bigger of the twins. The general condition of neither was satisfactory and they were in an incubator for 13 days. Following hospital discharge their development was retarded. They first stood up while holding to a railing at two years of age and began to walk at two and a half years. The mental development of the patient's brother, though also retarded, was much faster and he completed the ninth grade. He worked at various jobs but showed disturbing psychopathic and sexual trends and was finally admitted to a mental institution. At

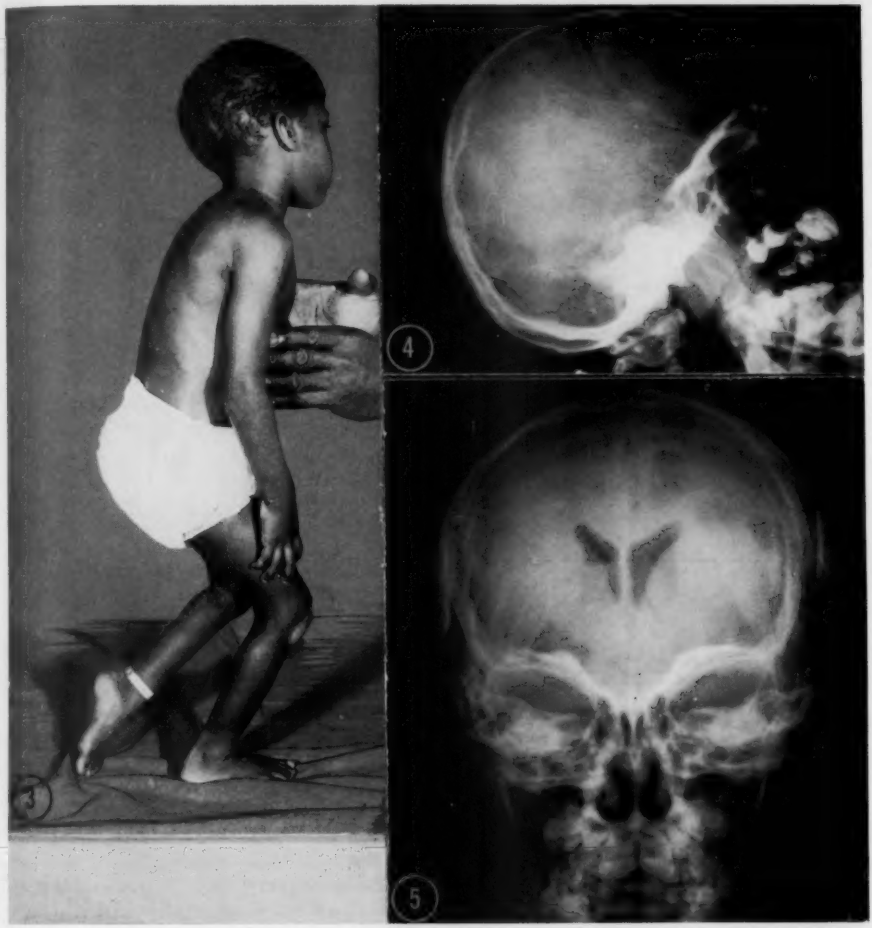

FIG. 3. *Case 2.* The patient is unable to stand without support. There are pronounced contractures of the left extremity.
FIG. 4. *Case 2.* Roentgenogram. Smallness of the head in lateral projection is apparent.
FIG. 5. *Case 2.* Normal pneumoencephalogram except for slight dilatation of the ventricular system.

the age of 15 years the patient's intelligence quotient was 43 and he was placed in an institution for the mentally retarded.

Examination at the age of 28 years: General physical examination was normal. He was cooperative but self-conscious. His general interests were very limited and he grew nervous and impatient easily when asked to perform problems beyond his mental capacity. He spoke indistinctly, using a limited vocabulary. His intelligence quotient was 51. The cranial nerves were normal, except for slight esophoria. Muscle strength was good, but skilled movements were generally awkward. He walked normally, but running was defective. Sensory, cerebellar, and reflex examinations were normal.

Laboratory examinations were normal, as was an electroencephalogram. Roentgenograms of the skeleton and spine were normal. Films of the skull showed a thick calvarium and marked calcification of the anterior portion of the falx.

Comment: It was not possible to obtain detailed data regarding maternal diabetic manifestations during pregnancy, which took place nearly 30

years before. In spite of high insulin intake, nearly all of her blood sugar estimations were elevated. The additional metabolic stress resulting from pregnancy might have disturbed her diabetes further. It is interesting that two other siblings were mentally dull, in addition to the mentally defective patient and his twin brother who was also slow. The interpretation of the pathology and pathogenesis in this instance is difficult. As in case 3, occurrence of a disturbance on the neuronal level in a late gestational stage can be postulated.

Case 5. The patient's mother developed diabetes in 1948 at the age of 29 and was controlled with moderate doses of insulin and diet. In December 1950 and in March 1951 she had episodes of severe diabetic acidosis and coma. In April 1951 she became pregnant. Very little is known regarding the course of her pregnancy, except that her diabetes remained poorly controlled. Just prior to the delivery, however, diabetes was brought under strict supervision. She went into labor spontaneously in the eighth month of pregnancy and was delivered by low forceps. The child, a girl weighing 5 pounds and 8 ounces, showed multiple congenital malformations. She had to be resuscitated and was given oxygen and incubator care, but she expired nine hours after birth.

The postmortem examination revealed the following congenital anomalies: bilateral cleft lip and cleft palate, syndactyly of both hands, patent interventricular septum, absent gallbladder, absent hepatic bile ducts, and severe malformation of the brain. In addition, there was partial atelectasis of the lungs and aspiration of amniotic fluid. No definite gross or microscopic abnormality in the pancreas was noted.

The calvarium and the dura were normal. The brain was grossly malformed and weighed, together with the brainstem and the cerebellum, only 54.3 gm. When viewed from the dorsal aspect, it showed a rudimentary cerebrum in the most anterior and lateral location (figures 6 and 7). Fused hippocampal gyri in the form of a horseshoe structure bordered the posterior extremity of the brain (figures 8 and 9). From the hippocampal gyri posteriorly up to the tentorium cerebelli there was a cavity filled with yellowish fluid. This cavity was covered superiorly by meninges and small basal ganglia were situated on its floor. The olfactory bulbs and tracts, as well as the corpus callosum, were absent. The brainstem and the cerebellum were small and of usual configuration, except that no pyramids were present in the medulla.

Microscopically the striking feature was the presence of a rather extensive germinal layer, as well as scattered germinal nests, particularly in the subependymal zone of the brain. The basal ganglia and thalamus were identified but they were smaller than normal, distorted, and in an abnormal position. The histogenesis of the cortex corresponded to about the seventh to eighth month of gestation. No obvious neuronal destruction or inflammatory changes were present in the nervous parenchyma. This very complex malformation of the brain is classified as cerebral hypoplasia and arrhinencephaly.

Comment: The mother suffered from severe diabetes and was twice in diabetic coma. During pregnancy her diabetes remained poorly controlled. The prematurely born infant exhibited multiple congenital malformations, particularly of the brain. The analysis of malformations of the brain indicates that the disturbance of development must have occurred not later than the fifth week of gestation, before the more advanced differentiation of the prosencephalic vesicle takes place.

DISCUSSION

All four patients who were studied clinically had severe mental deficiency. Two of them (cases 1 and 2) showed congenital cerebral diplegia. In the two remaining patients (cases 3 and 4), apart from marked impairment of intellect, there was no gross deficit of somatic function, and they may be classified as having primary mental retardation. The fiifth patient, whose state was not compatible with life, showed severe congenital malformation of the brain and other organs.

Since the presumptive pathogenesis and pathology in each individual patient has been considered, only a general analysis of the possible causative factors will be attempted. In all five patients the abnormality involving the central nervous system must have occurred during prenatal life. The control of maternal diabetes during pregnancy was quite inadequate in all instances, particularly in mothers of the most severely affected patients (cases 1, 2, and 5). Obviously, the association of diabetes mellitus in these mothers and neurologic abnormalities in their offspring cannot be taken as conclusive proof of a causal relationship. This is particularly so, since it is well known that many normal infants are born to diabetics. Nevertheless, the hypothesis that a certain proportion of fetuses are damaged by the disturbance of maternal metabolism during diabetes is warranted. Such a hypothesis is further strengthened by data obtained from experimental studies and also by the high mortality rate of infants born to diabetic mothers. Before attempting to analyze the potential factors affecting prenatal development in offspring of diabetic mothers, certain contributions of general importance need to be stressed. One of these relates to the fact that various noxious factors cause predominant damage to those

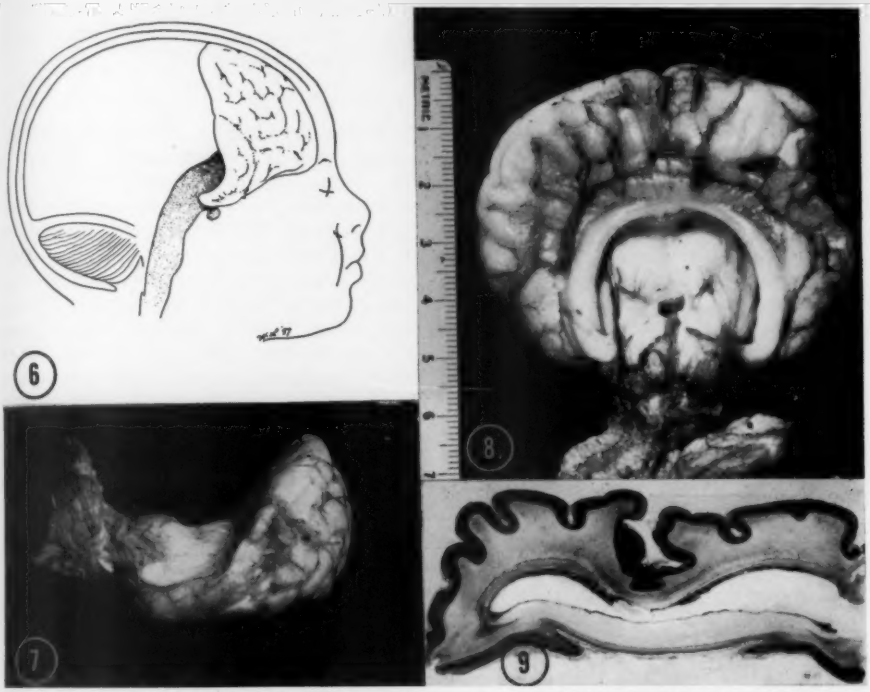

FIG. 6. *Case 5.* The drawing of intracranial content as seen at autopsy. Posterior to rudimentary cortex there is a large cavity filled with fluid.
FIG. 7. *Case 5.* Lateral view of the brain and brainstem (the base of the brain is lying on the table and the dorsal portion is exposed).
FIG. 8. *Case 5.* View of the posterior and superior aspect of the brain. Note conjoined hippocampi in the form of horseshoe structure.
FIG. 9. *Case 5.* Stained coronal section through the cortex and hippocampi. Note the presence of cellular heterotopias in subependymal region and almost normal thickness of the cortex.

developing structures which happen to be in the most sensitive stage for the action of the particular agent. This is true for the deleterious action of ionizing radiation and certain enzymatic inhibitors, as well as excessive concentration of abnormal metabolites or exogenous toxins.[17,18] Also, a deficiency in the basic substances necessary for tissue metabolism during rapid growth may impair normal development and produce various abnormalities.[18,19] Another important finding concerns the fact that the same noxious factors acting during various stages of development can produce different morphologic abnormalities.[20]

What are the noxious factors which can be implicated in disturbing normal development of the fetus in a diabetic mother? Admittedly, states of acidosis, hypoglycemia, and hormonal imbalance must be considered. Pronounced diabetic hyperglycemia is frequently associated with a severe degree of ketosis. It has been established[21] that ketone bodies pass the placental barrier and may accumulate in dangerous levels in the fetal blood. Also, it was shown that, in diabetics with a high blood concentration of ketone bodies, there is a reduction of cerebral respiration ranging from 20 to 50 per cent of the total value.[22,23] This state is associated with an alteration of consciousness ranging from mild confusion to coma. It is unknown to what extent cerebral metabolism of the developing fetus may be affected by high concentration of ketone bodies. However, considering the rapid growth and differentiation of the immature neural elements, the requirement for tissue respiration must be great. It

is also known that, at various stages of brain development, different structures have faster metabolism and so are more vulnerable.

Experimental studies of Lichtenstein and coworkers[24] and Hicks[25] have shown that hypoglycemia is capable of injuring developing neural elements and in this way producing damage and various malformations of the brain. Less is known regarding the disturbance of anterior pituitary and adrenal hormones in diabetics. However, the occurrence of oversized babies in diabetic and prediabetic mothers suggests that there is an imbalance of growth hormone. Irrespective of which of these mechanisms may be most frequently incriminated in the disturbance of fetal development in the diabetic mother, certain general impressions can be formulated. It would appear that, in addition to an increased mortality rate, the offspring of diabetic mothers also have an increased morbidity risk. The latter may be manifested by neurologic abnormality, mental deficiency, or both conditions. In this paper evidence has been brought forward showing that congenital malformations occur in a proportion of these cases, but further studies are needed to reveal the underlying pathologic changes in the other clinically abnormal infants.

SUMMARY

There is satisfactory evidence that the incidence of fetal death in diabetic mothers is very high. Similarly, the rate of congenital malformations, as estimated from autopsy findings, is greater than in the normal population. It is suggested that the incidence of morbidity due to involvement of the central nervous system in the surviving offspring of diabetics is also higher than in children born to nondiabetic mothers. The chief clinical abnormality in all four surving infants described in this paper consisted of a severe degree of mental deficiency. Cerebral diplegia was also present in two of the patients. The fifth patient had pronounced malformations of many organs, particularly of the brain, which were incompatible with life. The nature of the cerebral abnormalities found in infants without prenatal malformations needs further investigation.

The authors are indebted to Dr. Paul Yakovlev for his generosity in permitting us to include case 5.

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Celontin in patients with refractory epilepsy

Robert S. Dow, M.D., Jean P. Macfarlane, M.D. and Janice R. Stevens, M.D.

DESPITE the many available anticonvulsant medications and the excellent effects obtainable, control of seizures in certain patients, especially those with "minor" epilepsies, remains a problem. One of the newest anticonvulsant drugs is Celontin (N-methyl-a, a-methylphenylsuccinimide) — a close relative of Milontin (N-methyl, 5-phenylsuccinimide). Recent reports have indicated some benefit from Celontin in petit mal epilepsy,[1–3] in partial motor and psychomotor attacks,[4] and in mixed epilepsy.[5]

This is a report on the use of Celontin in 62 patients, all of whom were selected because of refractoriness to previous extensive therapy with maximal doses of various combinations of other medications. These patients had all had a trial of previous anticonvulsant therapy. Only four patients had used Dilantin and phenobarbital exclusively. Fifty-eight patients had been on four or more drugs, and over half of the group had already had a trial on six to 11 previously available drugs, at one time or another, including bromides, phenobarbital, Dilantin, Mesantoin, Mysoline, Hibicon, Phenurone, Milontin, Tridione, Paradione, Thiantoin, and Diamox. These drugs were usually carried to toxic levels and in varying combinations without satisfactory control of all seizures, especially the minor or partial varieties. All remained difficult therapeutic problems.

PATIENT MATERIAL AND METHODS

The 62 patients in this study were seen in private practice, in the University of Oregon Medical School clinic for convulsive disorders, and in the U. S. Veterans Administration Hospital in Portland, Oregon. They ranged in age from two and a half to 68 years; 18 were under age 15, and 44 were 15 years or older. There were 31 males and 31 females. Duration of epilepsy before Celontin therapy varied from one year to more than 60 years. Many types of seizures were represented and a large number of patients had a history of several varieties (table 1). However, grand mal seizures were well controlled in most cases and the "minor" or partial attacks represented the therapeutic problem. As noted above, all patients had responded poorly to previous extensive and intensive therapy.

Dosage of Celontin varied from 0.3 to 1.2 gm. daily and was usually 0.3 gm. three times a day in the adults. Duration of treatment ranged from only a few days to a maximum of 28 months. Twenty-one patients took Celontin for six months or longer and 13 patients are still under therapy. With very few exceptions, the drug was added to or substituted for only part of the previously partially ineffective medication.

RESULTS

The results of Celontin treatment are summarized in table 2. In eight patients the trial was too brief to permit adequate evaluation of the effect on the seizure pattern. Of the remaining 54 patients, complete control was obtained in six (one out of ten patients with abortive grand mal seizures, two of 22 with petit mal seizures, and three of 13 with focal attacks other than the psychomotor type). Practical control or marked improvement was attained in others (four with petit mal, one with psychomotor attacks, and one with focal attacks other than psychomotor). A number of other patients appeared temporarily improved, often to the point of practical to complete control for periods of several months, but then returned to their former status. Other patients showed little or no sustained benefit. Five patients reported an increase in seizures while on Celontin.

Two case reports indicate the improvement seen in some patients:

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TABLE 1

TYPES OF SEIZURES IN 62 PATIENTS TREATED WITH CELONTIN

Grand mal only	4
Petit mal only	9
Psychomotor only	5
Other focal seizures	8
Mixed types—	
Grand mal and petit mal	10
Grand mal and psychomotor	15
Grand mal, psychomotor, and petit mal	3
Grand mal and focal	5
Psychomotor and focal	1
Petit mal and focal	1
Infantile spasms	1
	62

Case 1. A three year old boy was born prematurely at seven months gestation. Motor development was very slow and, when first seen here at 22 months, he was unable to sit and showed internal strabismus, marked spasticity of all extremities, and myoclonic jerks occurring every few minutes. No other types of seizures had been observed. An electroencephalogram was diffusely abnormal, with multiple spikes and slow waves. Numerous anticonvulsants were tried without benefit, including Mebaral, Tridione, Paradione, Milontin, Dilantin, Phenurone, Diamox, and Peganone. In November 1955 Celontin was begun and gradually increased to 0.3 gm. three times a day (as the sole medication). At first, difficulty was encountered in giving the child his medication and, with the lower, erratic dosage, reduction of seizures was estimated at 50 to 75 per cent; with present full dosage he has no attacks. No other undesirable effects have been noted. Sedation develops with higher dosage of 1.2 gm. daily. At three years this child can still only sit but he uses simple sentences.

Case 2. A seven year old girl has had both petit mal and grand mal seizures since age three. She is mentally retarded, with an estimated I.Q. of 40 to 50, and shows very hyperactive, immature behavior. Electroencephalograms have shown almost continuous diffusely abnormal activity, with two to three per second spikes and waves and multiple spikes. Her seizures were uncontrolled and frequent, occurring many times daily, despite extensive therapy (Tridione, Dilantin, Dexedrine, phenobarbital, Mebaral, Phenurone, Mysoline, and bromides). Celontin was started in March 1955 (in addition to Tridione and Mebaral which she was already taking). Improvement was dramatic and she has now been taking the drug (0.3 gm. three times a day, with Tridione and Mebaral) for 26 months. She has had no attacks for 23 months. No toxic effects have been noted, except for drowsiness early in treatment. Repeated white counts and urine urobilinogens have been normal. Her parents believe that she is greatly improved mentally, although psychometric studies have not confirmed this impression.

SIDE EFFECTS

The undesirable effects possibly due to Celontin are summarized in table 3. Almost half the patients noted some side reaction, mostly minor.

Two patients showed evidence of possible hepatic decompensation while under Celontin therapy. The relationship of Celontin to this finding is difficult to evaluate, but is suggestive.

In one patient cephalin flocculation, which was known to be negative one and two months after adding Celontin to Dilantin and phenobarbital, became positive after four months therapy. Anorexia and increased seizures appeared at the same time. Celontin was discontinued but restarted two weeks later because of continued frequent seizures. Two months later it was stopped because of ineffectiveness. The cephalin flocculation then was 2+, 3+, and was still 3+ four months later, without other laboratory or clinical indications of liver damage.

In the second patient the cephalin flocculation first became positive (2+, 3+) one week after adding Celontin to Phenurone and Dilantin (which she had been taking for many months previously). Phenurone was discontinued immediately and Celontin and Dilantin continued. The cephalin flocculation remained positive without other indications of hepatic

TABLE 2

RESULTS OF TREATMENT WITH CELONTIN IN VARIOUS TYPES OF SEIZURES IN 54 PATIENTS REFRACTORY TO OTHER THERAPY

Type of seizure	*Number of patients**	*Complete control*	*Practical control*	*Slight reduction*	*Temporary reduction*	*No effect*	*Worse*
Grand mal	10	1	0	3	1	5	1
Petit mal	22	2	4	3	3	7	3
Psychomotor	18	0	1	3	6	8	0
Other focal	13	3	1	0	3	5	1
Infantile spasms	1	0	0	0	0	1	0
		6	6	9	13	26	5

*Patients with two types of seizures appear twice in this table.

difficulty until five months after beginning Celontin therapy, when an attempt was made to gradually substitute Diamox for Celontin because of recurrent seizures. At this time the patient noted anorexia, light stools, and yellow sclerae. On her own initiative she resumed Celontin and discontinued Diamox, becoming symptom-free and seizure-free in a week. Cephalin flocculation following this episode was more strongly positive (3+, 4+), and right upper quadrant tenderness plus pruritic spider angiomata over the chest and extremities were noted. Complete blood count, prothrombin time, total protein, and albumin-globulin ratio were normal. Celontin was stopped two months later and Mesantoin substituted. Two months later the cephalin flocculation was still positive (2+, 3+), but bromsulfalein and other laboratory indices of liver function were normal and the rash had disappeared. Because of marked increase in seizure frequency, the patient was allowed to resume Celontin, which has been continued to the present time, with persistent 3+ cephalin flocculation test but still without other clinical or laboratory evidence of hepatic decompensation. She has continued to have one or two seizures monthly, a distinct improvement over the control periods on other drugs.

No other patients have shown clinical evidence of hepatic damage; repeated urine urobilinogens have been within normal limits from patients on long-term therapy.

Albuminuria (2+) and periorbital edema were noted in one 11 year old boy after 11 months of therapy. Celontin was discontinued immediately and the urine became normal. He has since shown anemia and skin and mucous membrane lesions suggestive of drug intoxication while on anticonvulsants other than Celontin, however.

Routine blood counts on patients on Celontin revealed no abnormalities.

Drowsiness and unsteadiness were the most frequent undesirable effects, each occurring in eight patients. Therapy was discontinued in a few of these patients but was generally continued at lower dosage.

Six patients developed personality changes. Four of these had a diagnosis of psychomotor or temporal lobe epilepsy. One of these was an acute psychotic episode requiring hospitalization. Another patient with a past history of behavior disturbances required commitment to a state hospital because of increased destructive behavior. The other reactions reported were minor and transient degrees of irritability. Other side effects and toxic reactions of minor degree are summarized in table 3.

TABLE 3

SIDE EFFECTS POSSIBLY ATTRIBUTABLE TO CELONTIN IN 29 OF 62 PATIENTS

Reaction	*Number of patients with reaction*	*Number in which drug was discontinued because of reaction*
Drowsiness	8	2
Unsteadiness	8	3
Headaches	2	1
Fever	1	1
Anorexia	1	0
Hiccoughs	1	1
Nausea	1	1
Vomiting	1	1
Personality changes	6	
Acute psychotic episode	1	1
Irritability	2	2
Alternately sleepy and wild	1	1
Behavior problem	1	1
Swelling of eyes	2	2
Swelling of eyes, hands, and wrist	1	1
Question of liver damage	2	2
2+ albuminuria	1	1
Skin rash	2	2
Total	37*	23

*separate reactions in 29 patients

DISCUSSION

Although many patients in this series showed no benefit, Celontin is useful because of the rather dramatic beneficial effect in a few very refractory patients. It seems most useful in partial seizures of various types which are notoriously difficult to control.

The suggestive evidence of hepatic damage in two patients and of renal damage in one patient is disturbing and has not been reported previously. This should be specifically looked for in the future. Carter and Malev[5] have reported normal liver function tests in 16 patients on Celontin. The serious psychic reactions seen in two patients indicate the need for careful selection and supervision, especially in patients with psychomotor epilepsy or a past history of personality disturbances.

Other side reactions were relatively frequent but not serious, consisting mainly of drowsiness and ataxia.

SUMMARY

Sixty-two epileptic patients with various types of seizures previously partially or totally refractory to former anticonvulsant therapy were treated with Celontin (N-methyl-a, a-methylphenylsuccinimide) in doses up to tolerance. In nearly all instances, the new drug was added to or replaced part of the previous maintenance medication. Of the 54 patients who received Celontin long enough for adequate evaluation, six patients achieved complete seizure control, six were distinctly improved, and five patients experienced an increase in seizure frequency on the drug. The remainder noted little or no improvement. Age, clinical seizure type, and electroencephalograph pattern bore little relation to the level of improvement. Principal side effects were sedation and ataxia, usually related to overmedication with Celontin or additive effect of Celontin with other anticonvulsant agents. Two patients demonstrated evidence suggestive of liver damage. Six patients noted undesirable psychic reaction, in two instances requiring hospitalization. Periorbital edema occurred in three patients, albuminuria in one, and skin rash in two individuals. Other side reactions were minor and transient.

It is felt that this drug is a useful addition to the therapeutic armentarium against the epilepsies, particularly in patients with residual abortive or minor seizures subsequent to fair control of major attacks.

Celontin was made available through the courtesy of Parke, Davis & Company as PM 396.

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■ In treating of the causes and method of cure of epilepsy, I shall consider the disease under the two general heads, *idiopathic* and *symptomatic*, the first a primary affection of the brain; the latter, that which has its origin in some other part of the system, and affects the brain secondarily.

Before I proceed to the consideration of the particular causes of idiopathic and symptomatic epilepsy, I wish to remark, that, in the list of general causes of the disease, some writers have mentioned supernatural agency, and the influence of the heavenly bodies. Many of the ancients believed that epilepsy is sometimes thus produced, and some eminent men in modern times seem to have been inclined to these strange opinions. Van Swieten observes, that it is by no means surprising, that a disorder attended with such horrible and various symptoms, should have been ascribed to supernatural causes; and he thinks that the disease may have been produced by such causes. In favour of this notion he relates a case, and makes a reference to Scripture.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Unusual form of cerebellar ataxia

Combined dentato-rubral and pallido-Luysian degeneration

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Nathan Malamud, M.D.

INCLUDED in the group of cerebellar ataxias is a great variety of disorders. They may be classified into the hereditary spinocerebellar form of Menzel, the hereditary cerebello-olivary degeneration of Holmes, and the sporadic olivopontocerebellar atrophy of Déjerine-Thomas.[1] Predominant involvement of the dentato-rubral system has rarely been observed, however, and that is why the following case is reported. Other features of interest in this case were combined degeneration of cerebellar and extrapyramidal systems and the unusual occurrence of Babinski's sign of cerebellar catalepsy.

CASE REPORT

A 63 year old Yugoslav salesman was admitted to the hospital in March 1952 with a history of increasing unsteadiness of gait over a period of five years. The onset was insidious and the course slow. People thought him drunk when they saw him walking. His wife remarked that whenever she would brush the top of his head "his eyes would open wide and he would jump." In 1950 he was hospitalized because of reactive depression over financial reverses. At this time his speech was noted to be of an "odd quality" suggesting neurologic disorder of unknown type. Examination of the cerebrospinal fluid and an electroencephalogram were normal. The family history was without significance. The patient was a veteran of World War I, having enlisted at the age of 14. He had been a sharpshooter and rifle instructor serving in the U. S. Army in the Philippines and Siberia from 1914 to 1920. He acquired syphilis in 1915, for which he received extensive treatment. There was no history of encephalitis or head injury. He drank alcohol moderately and did not smoke or use drugs.

On admission examination he appeared to be well nourished, showing none of the stigmata of vitamin deficiency, although he was said to have lost 30 pounds in weight since the onset of his present illness. There were many bruises about the chest and lower extremities, apparently from frequent falls. Blood pressure was 165/100, but otherwise the general physical examination was not remarkable. His speech was slurred, high-pitched, and uneven, with explosive outbursts. There was a constant motor restlessness of the body, particularly of the extremities, which had a choreoathetoid character. He was able to walk without assistance but was extremely ataxic. There was a tendency to fall backward, particularly when standing still, and it was apparent that he walked better when he speeded up his gait. There was marked unevenness in the length of his stride. He tended to lift his legs high and stamp them down, landing on his heels. The cranial nerves were normal; there was no nystagmus. There were grimacing facial movements. The finger-to-nose test was performed adequately, but the heel-to-knee test was extremely erratic bilaterally, with pronounced overshooting and oscillations of the foot in moving the heel along the shin. There were marked rebound phenomena and dysdiadochokinesia of the lower extremities. He was unable to sit up from a supine position unassisted. The Babinski test for cerebellar catalepsy was elicited (with the patient on his back, the thighs flexed and abducted on the trunk, and the knee joints flexed, after a few moments of wavering, an extreme degree of immobility would set in so that the patient maintained this position for an indefinite period of time without wavering or drifting of the lower extremities). There was no evidence of muscular atrophy or fibrillations. The tendon reflexes were active and equal; the knee jerks were pendular. There were bilateral Hoffmann signs but no Babinski toe sign or any of its confirmatories, the toes being maintained in maximal plantar flexion. The abdominal reflexes were active and equal. Sensory perception to all modalities was unimpaired. The patient was well oriented in all spheres. He had unprovoked laughing and crying spells, but there was no psychotic content in his thought processes. He scored an I.Q. of 98 on the full-scale Bellevue-Wechsler test, with scatter in the subtest scores indicative of a mild organic mental impairment.

Laboratory examinations, including blood serology, hemogram, and urinalysis were normal. The cerebrospinal fluid was under a pressure of 110 mm. water, contained 2 cells per cu.mm. and 25 mg. of protein per 100 cc., and showed a negative Pandy, negative Wassermann, and a gold chloride reaction of 0000000000. A pneumoencephalogram showed a normal ventricular system but a moderate increase in subtentorial air.

From the Veterans Administration hospitals at Oakland and Palo Alto, California, and University of California School of Medicine, San Francisco, California.

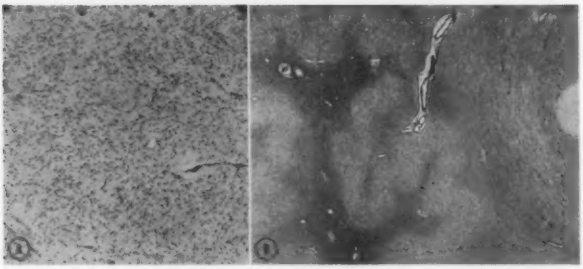

FIG. 1. *A.* Dentate nucleus, showing paucity of neurons and increase in glial elements. Nissl stain. *B.* Dentate nucleus, showing dense gliosis of central white matter and moderate gliosis of surrounding white matter. Holzer stain.

The course of his illness in the hospital was marked by gradual progression of disability. His speech became increasingly more unintelligible and his handwriting illegible. The choreoathetoid movements became more pronounced and wider in extent so that they resembled ballismus. They were less marked at rest. Whenever he tried to move any part of his body actively, the lower extremities moved upward, swaying in every direction. The eyeballs wandered in their orbits. Marked muscular hypertonicity set in, although it varied considerably from time to time. He became unable to walk even when supported; he was maintained in a wheel chair during 1953 and thereafter was bedridden. Toward the end he developed pneumonia and died on November 6, 1955, approximately eight years following the onset of his symptoms.

Postmortem examination. The general autopsy findings were bronchiectasis and bilateral bronchopneumonia of the aspiration type; mild chronic hepatitis, pancreatitis, and cystitis; and mild to moderate generalized arteriosclerosis.

The brain weighed 1260 gm. Partly organized thin subdural hematomas extended from the superior sagittal sinus over both convexities. The brain was not compressed, however. The leptomeninges and basal arteries were not remarkable. There was no external evidence of cerebral atrophy. The cerebellum appeared slightly reduced in size and, together with the brainstem, it weighed 130 gm.; the pons and the inferior olives were of normal size.

Coronal sections disclosed a normal appearance of the cortex and white matter; the lateral ventricles were of average size. The globus pallidus was bilaterally atrophic and deep brown, whereas the striatum and thalamus were normal. The dentate nucleus was symmetrically shrunken and brown. There was a suggestion of atrophy of the brachium conjunctivum. The folia of the cerebellum were not atrophic and neither were any of the structures of the brainstem. The third and fourth ventricles were moderately dilated.

Microscopically, changes characteristic of a primary degenerative process were noted in a number of areas. These consisted of reduction in neurons, chronic degeneration of those remaining, and reaction by glia, predominantly of astrocytes and fibers, but also to some degree of microglia.

The lesions were distributed predominantly in the cerebellifugal and extrapyramidal systems.

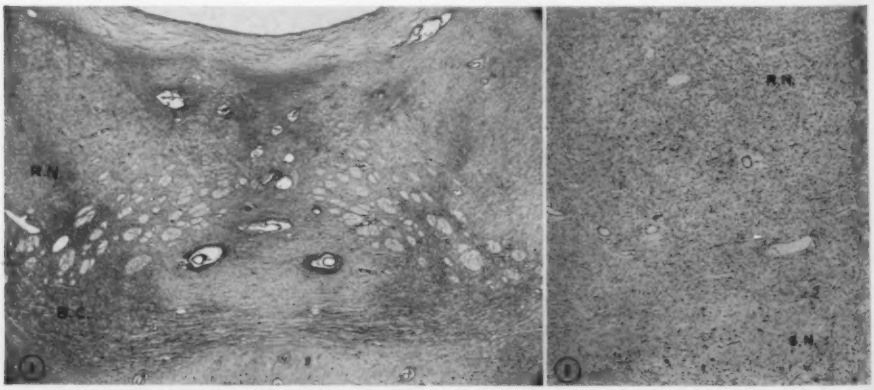

FIG. 2. *A.* Midbrain, showing bilateral gliosis of brachium conjunctivum (B.C.) at its decussation and of red nucleus (R.N.). Holzer stain. *B.* Red nucleus (R.N.) exhibiting paucity of neurons and substantia nigra (S.N.) containing scattered foci of degeneration. Nissl stain.

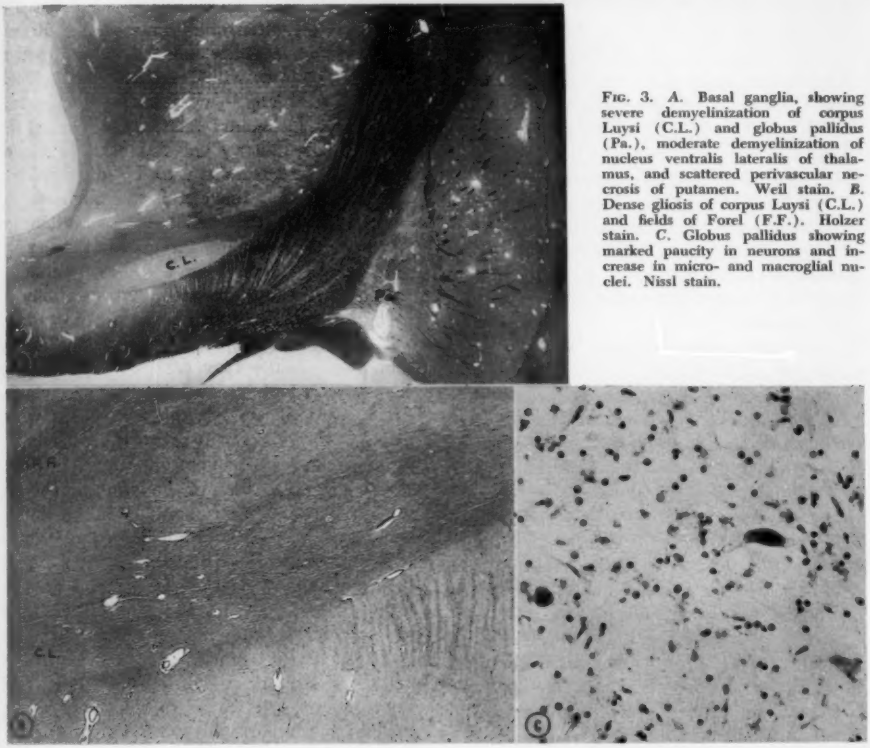

FIG. 3. *A.* Basal ganglia, showing severe demyelinization of corpus Luysi (C.L.) and globus pallidus (Pa.), moderate demyelinization of nucleus ventralis lateralis of thalamus, and scattered perivascular necrosis of putamen. Weil stain. *B.* Dense gliosis of corpus Luysi (C.L.) and fields of Forel (F.F.). Holzer stain. *C.* Globus pallidus showing marked paucity in neurons and increase in micro- and macroglial nuclei. Nissl stain.

Cerebellifugal system. The most striking changes occurred in the dentate nuclei. Here the majority of neurons had disappeared from all but a small dorsomedial area and were replaced by a marked increase in astro- and microglial elements (figure 1A). The central white matter of the dentate nucleus contained a dense network of glial fibers, while the fleece showed only patchy gliosis (figure 1B). In the gray matter of the cerebellum there was mild diffuse reduction in Purkinje cells, while the granular layer remained intact. The fibers of the brachium conjunctivum were severely demyelinated along their entire course. Replacement gliosis could be traced from the hilus of the dentate nucleus to the decussation in the midbrain (figure 2A) and beyond it to their termination in the red nucleus and thalamus. The red nucleus was severely involved on both sides. A diffuse increase of small fibrillary astrocytes in its substance and of glial fibers in its capsule replaced the degenerating neurons (figure 2B).

By contrast to the severe involvement of the cerebellifugal system, the cerebellipetal connections were virtually intact. There was only mild gliosis in the inferior olives and superficial transverse fibers of the pons, without any distinct paucity of neurons in the olivary or pontile nuclei or demyelinization of the inferior and middle cerebellar peduncles. The vestibular nuclei showed a moderate reduction of neurons and reparative gliosis. There were no changes in the spinocerebellar connections.

Extrapyramidal system. Of equal severity to the dentatorubral affection were changes in some parts of the extrapyramidal system. The corpus Luysi and the globus pallidus stood out sharply by their demyelinization from the surrounding structures (figure 3A). There was marked bilateral reduction of neurons in the corpus Luysi, to which corresponded a dense gliosis in the Holzer preparations (figure 3B). Both the lateral and medial segments of the globus pallidus bilaterally showed a marked decrease in neurons, with only a few shrunken or ghost forms remaining, surrounded by large numbers of glial nuclei (figure 3C). The substantia nigra contained only scattered areas of degenerating neurons, with released melanin pigment in gitter cells. There was severe degeneration of the fibers in the fields of Forel. There were no distinct changes in the caudate nuclei and pu-

tamen beyond a few perivascular foci of gliosis that appeared to be related to arteriolosclerosis.

The thalamus showed moderate degeneration that was confined to the nucleus ventralis lateralis at the site of termination of the fibers of the brachium conjunctivum. There were no discernible changes in the cerebral cortex, optic tracts, or spinal cord.

DISCUSSION

Three aspects of the case presented here require further comment, namely, 1) the pattern of cerebellifugal involvement, 2) the sign of cerebellar catalepsy, and 3) the association of degeneration in the extrapyramidal and cerebellar systems.

1. The most unique feature was the almost exclusive involvement of the cerebellifugal component within the cerebellar system. The majority of cases of cerebellar ataxia are spinocerebellar, olivopontocerebellar, or intracerebellar forms. In fact, Wilson[2] spoke of the cerebellifugal type as more of a theoretical possibility than an actuality. Greenfield[1] concluded that "no case of severe bilateral degeneration of the nucleus dentatus and superior peduncle, without degeneration of other spinocerebellar systems, has come to light in an extensive survey of the literature." As an example, the cases reported by Lejonne and Lhermitte,[3] Maas and Scherer,[4] Titeca and van Bogaert,[5] and Louis-Bar and van Bogaert[6] were cited. Dentato-rubral atrophy has been discussed in the literature in relation to a syndrome described by Hunt.[7] In this rare condition, which may be familial or sporadic, there is a combined symptomatology of cerebellar ataxia and myoclonus epilepsy. The pathologic findings in such cases as have been reported consisted of spinal cord and olivary changes, in addition to atrophy of the dentate nucleus. Some authors have attributed the myoclonus epilepsy to pathology in the dentate nucleus. However, Louis-Bar and van Bogaert[6] stated that, while myoclonus is always associated with atrophy of the nucleus dentatus, the reverse does not always hold. In our case, despite the clearcut involvement of the dentato-rubral system, there was no evidence of myoclonus epilepsy.

2. The clinical sign first described by Babinski[8] in 1902 and designated by him as "cerebellar catalepsy" was strikingly demonstrated in the present case. Except for occasional references by contemporaries of Babinski and two reports by American neurologists,[9,10] the sign has been forgotten or misunderstood. Recent textbooks have either omitted or confused it with catatonia or with "cerebellar fits." However, H. de Jong,[11] who has written extensively of experimental catatonia, described the "cerebellar catalepsy" of Babinski as a clinically rare phenomenon to be distinguished from catatonia. The test for cerebellar catalepsy requires the patient's cooperation, in contrast to the posture imposed by the examiner upon a stuporous or withdrawn catatonic patient. The test demonstrates the ability of certain patients with cerebellar disease to hold a static posture of the legs with statuesque immobility, while they cannot walk or move the legs through space without gross ataxia. Like the Romberg sign, this test serves, when positive, to differentiate between sensory ataxias and those of cerebellar origin.

The precise location of the lesion underlying this sign has been disputed. While Babinski avowed its cerebellar origin, Déjerine[12] stated that this lacked anatomic confirmation. Bing[13] reported that in his experience catalepsy has been observed only in tumors and abscesses of the cerebellum, and attributed the phenomenon to frontal lobe involvement consequent to increased intracranial pressure. Schaller[10] considered the sign of catalepsy, like that of asynergia, to represent distorted dynamic equilibrium, characteristic of a neocerebellar lesion, in the presence of conserved static equilibrium and preservation of the older parts of the cerebellum. Such an explanation might also apply to our case, since the phylogenetically newer ventrolateral part of the dentate nucleus was predominantly involved, while the older dorsomedial part was relatively preserved.

3. The occurrence of extrapyramidal signs in the spinocerebellar ataxias has been receiving increasing attention in the literature. It was first observed by Ley[14] in 1925, who reported a case with initial cerebellar and later parkinsonian signs. At postmortem examination, besides olivopontocerebellar atrophy, there was degeneration of the nucleus dentatus and superior cerebellar peduncle, to which Ley attributed the parkinsonian signs. Guillain, Mathieu, and Bertrand[15] found only olivopontine and spinocerebellar atrophy in a similar case and suggested that the cause of the par-

kinsonian rigidity was release of cerebellar efferents from control by afferent systems. In a more recent review of the literature, Rosenhagen[16] found, among 45 cases of ataxia, 25 with clinical evidence of extrapyramidal rigidity, in some of whom there were also choreiform movements. Autopsy disclosed lesions in the substantia nigra in 14 of these and changes in the basal ganglia in 11. It appeared, therefore, that the extrapyramidal signs had their basis in nigral or striatal lesions. Clinically, the extrapyramidal syndrome can precede, accompany, or follow the cerebellar symptoms or even remain latent. It has occurred in both heredofamilial and sporadic forms.

In our case there were no familial instances of the disease. The cerebellar symptoms appeared first and were followed only after some years by the extrapyramidal signs. Pathologically, although there was some involvement of the substantia nigra, the most severe changes occured in the globus pallidus and corpus Luysi, to which the progressive rigidity and ballismus could be attributed. Only two cases reported in the literature resembled ours to some extent.* André Van Leeuwen and van Bogaert[17] described a patient with initial cerebellar symptoms in whom terminally "the limbs were literally thrown in all directions as soon as she shut her eyes." At autopsy there was atrophy of the cerebellum, globus pallidus, corpus Luysi, and optic nerves. Titeca and van Bogaert[5] reported the case of a man, aged 47, whose sister had died of progressive cerebellar ataxia. Over a period of three years the patient developed ataxia, involuntary movements of wide range, and toward the end extreme rigidity. The pathologic findings were severe atrophy of the pallido-Luysian and dentato-rubral systems, gliosis of the white matter of the cerebrum and cerebellum, and degeneration of the inferior olives, pontine nuclei, and posterior columns. In other cases of this type the changes have been more widespread.[18,19] Thus, the combination of cerebellar and extrapyramidal signs has been so frequent as to suggest a common vulnerability of the two systems to some noxious agent. In the absence of more precise knowledge of etiology, however, this cannot be further defined.

*One of us (N. M.) is preparing for publication a case of hereditary cerebellar ataxia in which the pathologic findings were somewhat similar to the present case.

SUMMARY

1. A case of cerebellar ataxia with combined degeneration of the dentato-rubral and pallido-Luysian systems is reported.

2. The rare occurrence of exclusive involvement of the cerebellifugal system and the common association of cerebellar and extrapyramidal signs in the cerebellar ataxias are emphasized and the pertinent literature reviewed.

3. The significance of the Babinski sign of "cerebellar catalepsy," as demonstrated in the present case, is discussed.

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Cerebellar lesions after parenteral Dilantin administration

William W. Hofmann, M.D.

DIPHENYLHYDANTOIN (Dilantin) is an anticonvulsant drug whose worldwide use over the last 20 years attests to its safety and effectiveness. The compound has recently been made available commercially as an injectable solution for the control of difficult seizure problems in patients who cannot take oral medication and for the management of status epilepticus. The solution can safely be given intravenously or intramuscularly and produces a prompt response without depressing the function of the entire central nervous system, as do the barbiturates. Injectable Dilantin has been administered over 9,000 times by Murphy and Schwab,[1] who feel the agent is of great value in controlling almost all types of seizures without dangerous or prolonged side effects. All patients receiving the drug for a short period of time have responded quickly and favorably.

The purpose of this paper is to present evidence suggesting that large doses of Dilantin given over prolonged periods may produce certain pathologic alterations in the central nervous system. Our attention was drawn to the possible neurotoxic effects of this drug by microscopic studies on the brain of a young female patient who died during a relentless neurologic disorder accompanied by various types of seizures.

The patient was a 28 year old housewife who entered Stanford University Hospital on April 22, 1957, after having had four major convulsions in the preceding 24 hours. She had always been entirely well, except for recurrent brief "dizzy spells" during which she seemed confused for about a minute. These had been noted since the age of 13, but had never been investigated or treated.

About three weeks prior to admission she had developed a sore throat, some fever, and stiffness of the neck. She also complained of night sweats and a cough. She had not been exposed to any person with known neurologic symptoms or any of the exanthemata. Her malaise continued until the day before admission when, while riding in a car, she suddenly raised her right arm, turned her head to the right, and fell in a generalized seizure. This was followed by three more seizures on the way to a hospital. She was promptly given barbiturates (dose unknown), but upon awakening she again had several seizures. She was then transferred to this hospital.

Examination revealed a stuporous young woman with a stiff neck and a fever of 38° C. but no other general physical abnormalities. The blood pressure was 120/80 and pulse and respiration were normal. The reflexes were all brisk and the toe signs were bilaterally extensor, but there were no signs of increased intracranial pressure. The routine blood and urine studies were normal. The serum glucose was 104 mg. per cent and calcium 9.2 mg. per cent. The spinal fluid was under normal pressure, with no white cells and a protein of 52 mg. per cent. Cerebrospinal fluid cultures were sterile. Skull and chest films were normal. An electroencephalogram was not done.

During the first few hours the patient had recurrent partial seizures, with head turning to right or left and clonic movements in the right or left arm. She did not regain consciousness between these seizures. The episodes never lasted more than about 60 seconds, cyanosis was observed only twice, and respirations were unaffected during most of the seizures. Before treatment was instituted she had a total of about six such seizures.

Initial treatment consisted in the administration of 250 mg. of injectable Dilantin intravenously. This was followed by 250 mg. intramuscularly every four hours. The next day injections of 65 mg. of sodium phenobarbital were added to each dose of Dilantin. The patient's seizures stopped after the first dose of Dilantin, but she did not regain full consciousness at any time during her hospital stay. Four days after entry she was able to take oral fluids and responded verbally to simple questions.

The dosage of phenobarbital was eliminated after four days and the amount of Dilantin was slowly decreased. On the seventh hospital day partial seizures recurred, again without cyanosis or respiratory distress. These seizures were characterized by perioral twitching, some grimacing, and then clonic movements on one side or the other for 40 to 60 seconds. She again became stuporous and the temperature rose precipitously as high as 40.2° C. The temperature elevation was always treated promptly with sponging, icebags to axillae and groins, cold water enemata, and intravenous

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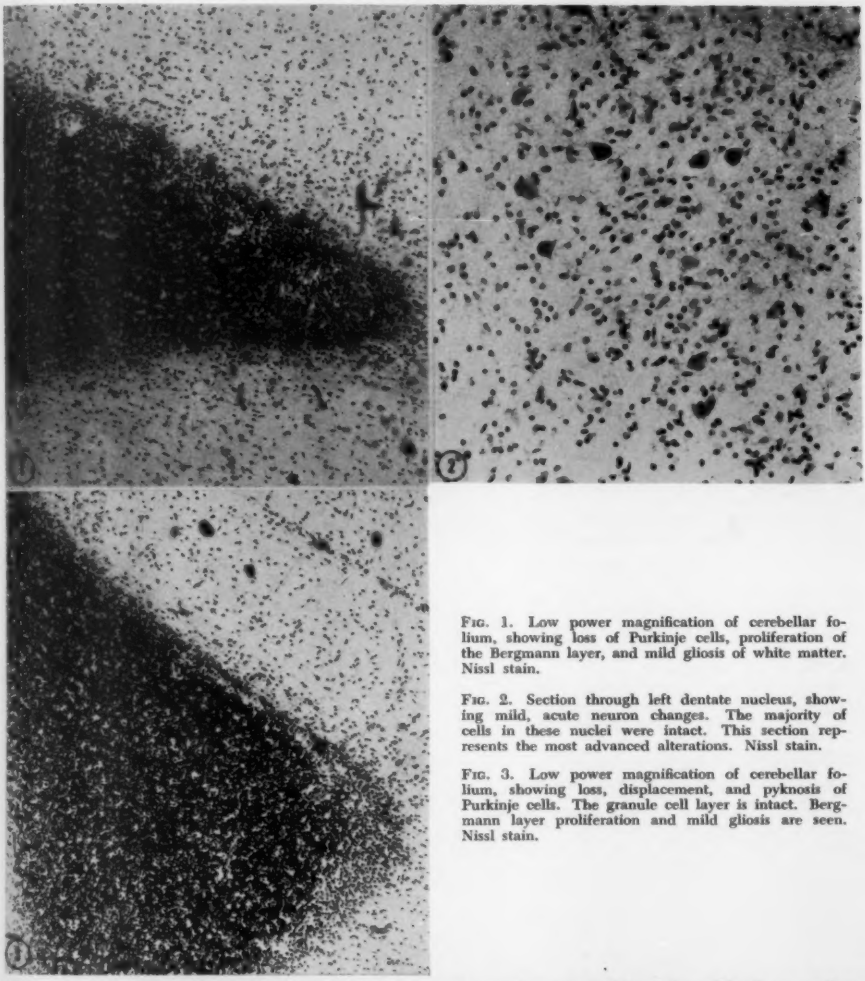

FIG. 1. Low power magnification of cerebellar folium, showing loss of Purkinje cells, proliferation of the Bergmann layer, and mild gliosis of white matter. Nissl stain.

FIG. 2. Section through left dentate nucleus, showing mild, acute neuron changes. The majority of cells in these nuclei were intact. This section represents the most advanced alterations. Nissl stain.

FIG. 3. Low power magnification of cerebellar folium, showing loss, displacement, and pyknosis of Purkinje cells. The granule cell layer is intact. Bergmann layer proliferation and mild gliosis are seen. Nissl stain.

fluids. The maximum continuous duration of fever over 39° C. was seven hours. Serum electrolytes were entirely normal on repeated examination.

On April 26, 1957 a systolic bruit was clearly heard over the left eye. Because of this finding and the past history of vertiginous episode, bilateral carotid angiograms were done. These studies showed no abnormalities.

The patient continued to have two to five seizures per day, despite increasing doses of phenobarbital (maximum 132 mg. every four hours by intramuscular injection) and continued injections of 250 mg. Dilantin every four to six hours. Antibiotics and parenteral fluids were given, though no organism was cultured from blood or cerebrospinal fluid. No improvement resulted.

On May 2, 1957 the patient's seizures changed. She no longer showed tonic and clonic movements, head turning, and so on, but developed frequent shivering movements with rigid extension of the legs and flexion of the arms. The neurosurgical consultant agreed that these represented decorticate spasms, but the patient still showed no signs of increased intracranial pressure. The barbiturates were again discontinued and Dilantin was decreased to 100 to 250 mg. intramuscularly every six to eight hours.

On May 3, 1957 Cheyne-Stokes respiration was

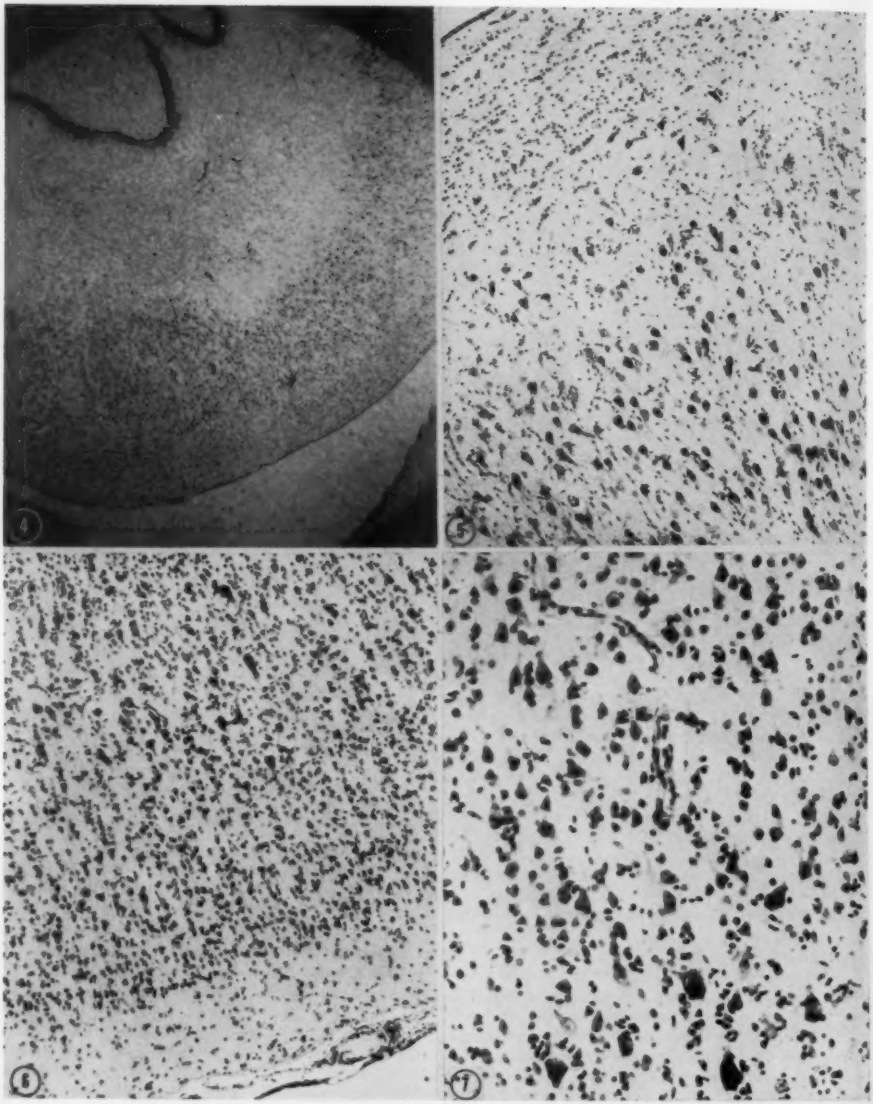

FIG. 4. Low power magnification of pyramidal cells in Sommer's sector, showing preservation of architecture. Temporal horn of lateral ventricle is at bottom right. Nissl stain.

FIG. 5. Higher magnification of cells in Sommer's sector. General architecture is normal. Neuronal changes are minimal. Ventricular surface is at top left.

FIG. 6. Low power magnification of structure of frontal cortex. Normal lamination and neuronal structure are quite well preserved. Nissl stain.

FIG. 7. High power magnification of frontal cortex, showing occasional acute swelling, tigrolysis, and loss of staining properties in neurons of layer 5. These changes were quite rare, and this section shows the most advanced alterations. Nissl stain.

noted. Bilateral parietal burr holes were made to rule out the still remote possibility of an expanding mass. The cortex fell away from the incision.

The patient deteriorated slowly, with frequent yawning, typical extensor spasms, and Cheyne-Stokes breathing. The blood pressure and pulse remained stable, but on May 8, 1957 respirations suddenly ceased.

Postmortem examination revealed no gross changes in the brain or any other organ. The microscopic studies of brain sections showed abnormalities in the basal ganglia, cerebellum, and, to a lesser extent, in the hippocampus, but these were not felt to be of sufficient magnitude to explain the patient's seizures or her death.

The most obvious and severe changes were found in the cerebellum, where the Purkinje cells had virtually disappeared. The cerebellar white matter, midline nuclei, and granule cells were essentially spared (figures 1 to 3). The neocortex was relatively intact and the hippocampal pyramidal cells, dentate fascia, and end-plate were surprisingly little damaged (figures 4 to 7). Mild neuronal changes, both acute and subacute, were seen in the caudate nucleus and thalamus with some perivascular round cell cuffing and mild gliosis (figures 8 and 9).

DISCUSSION

Interest in the clinical and pathologic alterations produced by Dilantin stems from observations of patients with ataxia or other cerebellar deficits following its use and from recent investigations by Utterback and co-workers[2] pertaining to the toxic effects in animals.

Many investigators [3–6] have reported slurred speech, nystagmus, and ataxia as a result of sensitivity to, or overdosage of, Dilantin. The studies indicate that any patient may show these signs, which may be quite insidious in onset. A few deaths have been attributed to the drug. Exfoliative dermatitis, though quite rare, is a very serious complication. The effects on cardiac muscle and conduction, while studied adequately in animals, have not been investigated completely in man and will be the subject of a future report.

Most of the effects of Dilantin overdosage are quite reversible upon withdrawal of the drug, but in an unresponsive patient the warn-

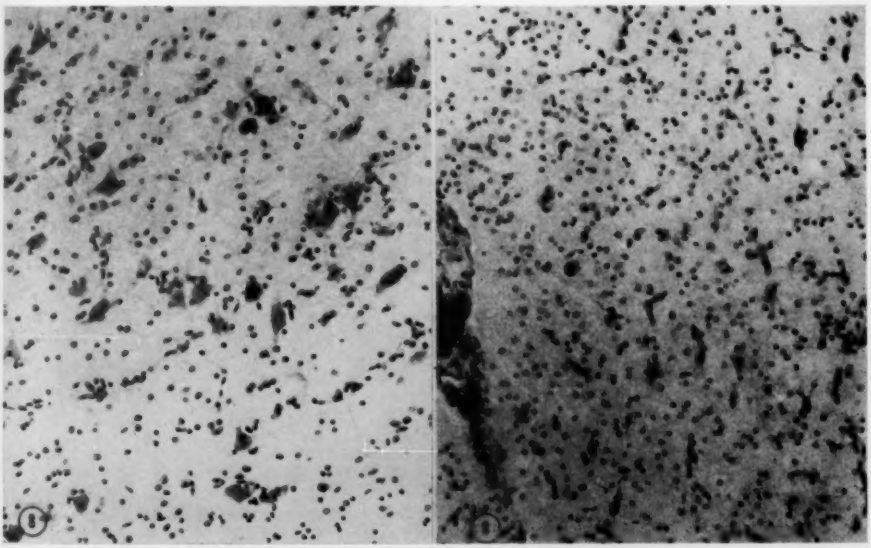

FIG. 8. Section through thalamus, showing acute nerve cell changes with swelling, nuclear displacement, and satellitosis. Mild gliosis is seen.

FIG. 9. Section through caudate nucleus, showing gliosis, perivascular round cell reaction, and subacute neurone changes. Slight ferrugination was noted in adjacent areas of the basal ganglia. Nissl stain.

ing signs may not be observed. Of course, the same problem exists with other compounds used to control seizures, especially the barbiturates. To date, only one report in the English literature has indicated that the clinical symptoms in man may be duplicated in animals and that these symptoms, while partially reversible, may be accompanied by definite lesions in the cerebellum.[2,8] These investigators have shown clearly that animals not subject to anoxia, seizures, or medication with any other drugs will develop severe loss of Purkinje cells, cystic gliosis of the cerebellar white matter, and damage to the granule cells if given Dilantin in daily doses of 15 to 30 mg. per kg. Our patient received 20 to 30 mg. per kg. for almost two weeks, and the cerebellar changes were qualitatively similar to those reported in animals.

The microscopic findings in the case reported here are not pathognomonic of any particular disease process or toxic agent. The location of the chief pathologic alterations brings to mind a good many etiologic possibilities, including anoxia, hypercapnia, hyperthermia, hypoglycemia, and perhaps simply repeated seizures. However, this patient's course in the hospital and some of the laboratory studies help to exclude certain factors.

Brief cyanosis was noted only twice; the seizures usually lasted only about 60 seconds, were frequently partial or focal, and were usually not accompanied by respiratory arrest for more than 10 or 20 seconds. The maximum number of such seizures was 12 in a 24-hour period. Suction was frequently used to clear the upper airway and very little mucus was obtained. At autopsy the trachea, main bronchi, and lungs were clear. The vital signs were measured almost hourly and the systolic blood pressure never dropped below 110 mm. Hg. Temperature was greatly elevated (over 103° F.) for a total of 32 hours during the entire illness. Serum calcium and glucose were normal.

Those factors known to damage the cerebellum and other areas of the brain were controlled as well as possible in this case. The extracerebellar structures, usually heavily damaged by anoxia, prolonged seizures, high temperature, and so on, were relatively spared when compared with the devastation of the Purkinje cells. These data, plus the fact that the patient received large doses of a compound known clinically to affect cerebellar function adversely, suggest quite strongly that the Purkinje cell destruction was due at least partly to Dilantin. The neuronal, glial, and perivascular changes in the basal ganglia might well result from premortem respiratory difficulties, but the round cell infiltration noted about a few of the smaller vessels suggests that a mild, subacute encephalitic process may have been a factor in the genesis of the patient's original seizures.

The speculations here regarding Dilantin toxicity should in no way detract from the usefulness of this drug, provided dosage precautions are respected. The work of Murphy and Schwab[1] clearly reveals the great value of parenterally administered Dilantin, and it should be obvious that a compound which will control most seizures without depressing respiration or leaving the patient in coma deserves a favored place in treatment.

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Behavioral changes following discrete lesions of temporal lobe structures

Charles D. Wood, Ph.D.*

THE PAPER on "A Proposed Mechanism of Emotion" by Papez[1] stimulated much interest in the rhinencephalon. Kluver and Bucy[2] reported on a group of bilateral temporal lobectomized monkeys and observed the following behavioral changes: psychic blindness, oral tendencies, hyperactivity, and emotional, sexual, and dietary changes. These results have been confirmed on cats[3] and in a bilateral temporal lobectomized human being.[4] Anand and Brobeck[5] failed to produce any of these behavioral changes on similarly operated rats, with the exception of placidity. Other findings,[6] however, were at great variance with the results of Kluver and Bucy[2] in that they reported "sham rage" resulting from bilateral ablation of the amygdaloid complex. Rage reactions have also been reported by other investigators.[7]

In bilateral temporal lobe ablation, large cortical areas and a number of subcortical cellular masses are removed. The conflicting behavioral changes reported from the various temporal lobe ablation studies may be a result of varying degrees of damage to the temporal lobe structures. If such differences are to be resolved and various behavioral changes assigned to definite structures within the temporal lobe, a program of discrete electrocoagulation and stimulation of these individual structures is necessary. The findings reported in this paper are the result of observations limited to the first portion of such a study.

The amygdaloid complex in the cat can be divided into six distinct nuclear masses. These nuclei are designated according to their relative position as cortical, medial, central, basal medial, basal lateral, lateral nuclei, and the intercalated masses[8] (figure 1).

METHOD AND MATERIALS

In the study on behavior 29 cats were used. Another 12 cats were prepared for stimulation with permanently implanted electrodes.

The animals were operated under sterile conditions with 25 mg./kg. Pentobarbital as the anesthetic. The Labtronics model 4 stereotaxic apparatus served as a head holder during the operations. A coronal skin incision was made and the underlying temporalis muscle and periostium reflected. A small trephine opening was made in the skull in the area indicated by the stereotaxic coordinates. Stainless steel bipolar electrodes, insulated except at the tip, were positioned in the desired subcortical area by means of the stereotaxic apparatus. Coordinates used in this study for the amygdaloid complex were L4 to 11, H −2 to −6, and S 13 to 15.[9]

Each animal in the behavioral group was observed for a control period of two to four weeks before operation. Bilateral lesions were then produced in the desired areas by electrocoagulation. A direct current of 1 to 7 milliamperes was applied for 30 seconds, utilizing a Grass S4 stimulator monitored with a Simpson volt meter. The electrodes were withdrawn and the incision closed with surgical silk. Eight control animals were operated on in the same manner, except that no coagulation current was used.

The bipolar electrodes were permanently fixed to the skull with acrylic plastic in the animals prepared for stimulation studies and insulated wire leads were brought through the skin at the back of the neck. The incision was closed with surgical silk. Stimulation currents varying from 3 to 10 volts (60 c/sec., 2.5 m.sec.) were used. During the course of the stimulation the animal was free to move

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about the room with light stimulation leads attached to a collar.

No special postoperative feeding or other care was necessary, with the exception of antibiotic injections; 1 cc. of procaine-penicillin G 300,000 units/cc. was given at operation and 0.5 cc. on the two successive days.

All lesions and stimulation points were determined histologically. Frozen sections of 50 μ were stained with cresyl-violet for cell studies and with Weil's stain for tract studies. Electrode placements were confirmed by the ferrocyanide method in the stimulation studies.[10]

RESULTS

Behavior

Behavioral changes resulting from discrete lesions placed bilaterally in the individual nuclei of the amygdaloid complex are as follows:

Hypersexuality. Bilateral lesions of the lateral amygdaloid nucleus produced hypersexual activity in two of five male animals and four of six female animals. The hypersexed state appeared after a period of eight to ten weeks following operation. Sexual changes did not result from bilateral lesions of any other structures in the temporal lobe area and were not produced by unilateral lesions of the lateral nucleus. Bilateral lesions damaging a small area of the lateral nucleus in four cats gave only a transitory hypersexuality. The hypersexed state was more pronounced when the greater part of the lateral nucleus and the ventral claustrum were destroyed. Lesions limited to the ventral claustrum in four cats failed to produce increased sexual behavior. The male cats demonstrated hypersexuality by determined efforts to copulate with other cats in the room regardless of sex. This sexual activity was continuous for periods of over an hour and ceased only with successful copulation. The animal then temporarily reverted to a normal state showing none of the other components of the temporal lobe syndrome. The females were normal friendly cats immediately following the operative procedure. After eight to ten weeks, however, they became withdrawn, sulked in the back of their cages, lost appetite, and responded little to petting. When released for observation, they avoided other cats by hiding in a corner or returning voluntarily to their

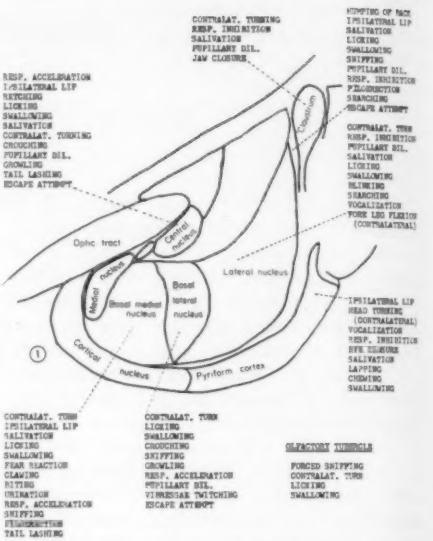


FIG. 1. Coronal section through the amygdaloid complex 13.5 mm. anterior to the interauricular line, summarizing the responses obtained by electrical stimulation of the individual nuclei.

cages. No precopulatory courting activity was displayed,[11] and, when the hypersexed males approached, the females would often spit at them. When the neck grasp had been accomplished by the males, the mating crouch was assumed by these females and treading activity was displayed. Normal postcopulatory activity was always displayed. This receptive state existed for two to three months and was terminated only when the animals were sacrificed. The normal males displayed no sexual interest in the receptive females.

Emotional changes. Bilateral lesions of the basal nucleus in five of ten animals and of the central nucleus in four of ten animals produced increased aggressive behavior. Growling, biting, and clawing were elicited by even gentle handling. Some animals would continue to growl even while they gave signs of enjoying petting. Other cats that approached were attacked and at times the aggressive cats would cross the room in order to attack them.

Oral tendencies. No oral tendencies were observed; a tendency to repeatedly examine all objects in the room by sniffing was seen in two cats with lesions of the central nucleus.

Dietary changes. A marked increase in food intake was seen in four of nine cats with lesions of the central and medial nuclei. The daily food intake was seen to quadruple, if allowed, and at times the paper on which meat was placed was chewed and eaten. This increased intake occurred even though the animals were under caged conditions and were not displaying hyperactivity.

Hyperactivity. Four animals with lesions placed in the medial nucleus displayed increased activity. However, approximately the same percentage of operated controls showed this activity after they had been under caged conditions for prolonged periods.

Psychic blindness. No evidence of psychic blindness or visual agnosia was seen in any of the animals in this study.

Stimulation

The stimulation results reported here are essentially in agreement with the findings of others.[12,13] Contralateral turning, licking, chewing, salivation, and swallowing were produced by stimulation throughout the temporal lobe region. Stimulation of the basal amygdaloid nucleus produced a fear or anger reaction, with running and jumping in a tight circle toward the side opposite stimulation. During this period, the animals growled, clawed, and bit themselves or the floor of the observation box, displayed piloerection, tail lashing, respiratory acceleration, and attempted to escape. In the central nucleus, stimulation evoked gastrointestinal responses, including retching, vomiting, and aerophagia. The emotional reactions observed in the stimulation studies of the basal nucleus were also obtained by stimulation of the central nucleus.

Stimulation of the lateral nucleus resulted in inhibition of the inspiratory phase of respiration, searching, vocalization, pupillary dilatation, and flexion of the contralateral forelimb. No fear or anger responses were elicited from this area.

Respiratory inhibition and strong jaw closure, as well as the usual oral responses, were produced by stimulation of the ventral claustrum.

Stimulation responses obtained from the external capsule were respiratory inhibition, piloerection, arching of the back, searching, and the oral responses.

Forced sniffing was seen when the olfactory tubercle was stimulated in one cat. As the animal turned contralateral to the side of stimulation, it carefully sniffed along the floor. This behavior was repeated each time the animal was stimulated.

The stimulation results are summarized in figure 1.

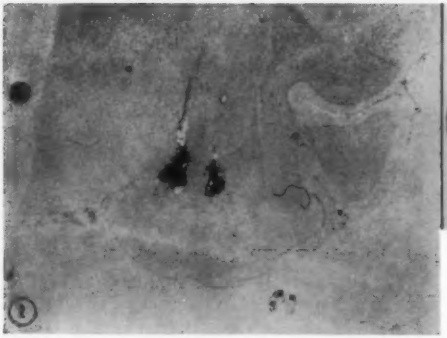
DISCUSSION

The behavioral changes previously reported following bilateral temporal lobectomy are the result of removal of a large cortical area and a number of subcortical structures. The results of this study indicate that these behavioral changes may be localized to definite subcortical cellular masses of the temporal lobe.

Lesions placed bilaterally in the lateral nucleus of the amygdaloid complex produced a hypersexed state after a period of eight to ten weeks. The delay would suggest retrograde degeneration of a related structure, and the resulting hypersexed state could be a release of the inhibiting influence of that system.

Electrical stimulation of the central and medial nuclei has been reported to cause ovulation[14] and uterine contraction. Lesions of the same area produce abortion in the gravid cat.[15] Activation of the medial amygdaloid division appears to have a strong influence on normal sexual functions. This fact, along with the hypersexed state produced by lesions of the lateral nucleus, suggests that the two areas may have antagonistic influences on these functions. The altered sexual activities reported above might be the result of an altered balance in the influence of these two areas.

The ventral claustrum appeared to be functionally related to the lateral nucleus of the amygdaloid complex. The hypersexed state became more pronounced when bilateral lesions were placed in the ventral claustrum, as well as in the lateral amygdaloid nucleus. Stimulation responses obtained from the ventral claustrum were more closely related to those of the lateral nucleus than to those of the more mesial amygdaloid nuclei. These results give physiologic support to Macchi,[16] who stated that the ventral claustrum is anatomically related to the lateral amygdaloid nucleus.



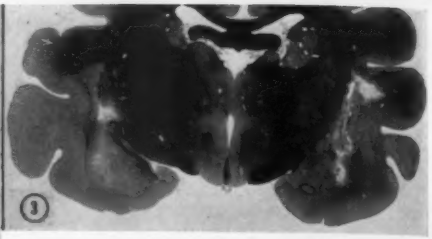


FIG. 2. Section through the amygdaloid complex showing localization of stimulation points which produced the anger or fear response (ferrocyanide method). FIG. 3. A representative section showing lesions of the lateral amygdaloid nucleus and ventral claustrum which produced hypersexual activity (Weil stain).

Increased aggressive behavior resulted from bilateral lesions of the central nucleus. These animals became increasingly aggressive to other animals and to the observer. Cats which were friendly prior to the procedure became difficult to handle and would attack other cats without provocation. Stimulation of this area produced a fear or anger reaction. The animals would bite their flanks, growl, and claw the floor of the observation area. This response was also obtained by stimulation of the basal nucleus. Although not all of the above evidence supports this supposition, the central and lateral amygdaloid regions may also balance one another in their influence on emotional reactions, as was proposed for the sexual reactions. Further investigation of this point is required.

Bilateral lesions of the central amygdaloid nucleus produced an increased food intake. This was the only area from which such a response was obtained. Stimulation of this structure evoked gastrointestinal responses such as retching, vomiting, and aerophagia. These results would indicate that the central nucleus is the structure concerned with gastrointestinal responses reported from the amygdaloid complex. Increased aggressive behavior was also seen when this structure was ablated electrolytically, and a fear or anger response was obtained when it was stimulated electrically. Due to its inaccessibe location in the cat, this structure was very likely not removed in some ablation studies. Some of the conflicting reports in the literature may be the result of different degrees of damage to this structure.

Gloor[17] has reported that impulses from the amygdala to the ventromedial hypothalamic nucleus arise only from the medial amygda-

TABLE 1

A COMPARISON OF RESULTS OF SOME OTHER INVESTIGATIONS OF THE TEMPORAL LOBE STRUCTURES

	Kluver & Bucy[2] (1938)	*Schreiner & Kling*[3] (1953)	*Terzian & Ore*[4] (1955)	*Anand & Brobeck*[5] (1952)	*Bard & Mountcastle*[6] (1949)	*Spiegel, Miller, & Oppenheimer*[7] (1940)	*This Study*
Animal	*monkey*	*cat*	*human*	*rat*	*cat*	*cat*	*cat*
Visual agnosia	yes	yes	yes	no	—	—	no
Oral tendencies	yes	yes	no	no	—	—	no (sniffing—central nucleus)
Hyperactive	yes	yes	yes	less active	—	yes	same as controls
Hypersexed	yes	yes	yes autosexual homosexual	no	no	—	yes (lateral nucleus and ventral claustrum)
Dietary changes	yes	—	yes	no	—	—	yes (central nucleus)
Emotional changes	placid	placid	aggressive	placid	aggressive	aggressive	aggressive (central nucleus and basal nucleus)

loid division. Lesions of this area may partially interrupt the afferent supply to the ventromedial hypothalamus and thereby produce emotional alterations.

No behavioral changes were produced by discrete lesions of the pyriform cortex. Stimulation of this area produced the oral responses found throughout this region (figure 1).

Oral compulsion was not produced by discrete lesions of any of the above structures. In two cats with lesions of the central nucleus, examination of all objects in the room by careful sniffing was observed. This behavior in cats may be analogous to the oral compulsion reported in monkeys.

The psychic blindness or visual agnosia that has been reported[2-4] may be due to extensive damage produced by bilateral temporal lobectomy. This condition was not produced by discrete lesions of any of the structures investigated here.

This study indicates that behavioral changes can be produced by discrete lesions of the subcortical cellular masses of the temporal lobe. The behavioral changes may give some suggestion of the physiologic function of these structures. Further studies of the functional anatomy and anatomic connections of the temporal lobe are necessary if this area is to be more fully understood.

SUMMARY

Results of this study indicate that some of the component parts of the temporal lobe syndrome can be localized to definite nuclei of the amygdaloid complex.

Discrete bilateral lesions of the lateral amygdaloid nucleus produced a hypersexed state after a period of eight to ten weeks following operation. This hypersexed state was intensified if lesions were also placed in the ventral claustrum. Stimulation of these structures failed to produce any of the emotional behavior reactions reported from the amygdaloid complex. Stimulation of the basal nucleus produced a fear or anger response. Bilateral lesions of the central amygdaloid nucleus resulted in increased aggressive behavior and also increased food intake. Stimulation of the structure produced a fear or anger response and gastrointestinal responses. Hyperactivity was seen in cats with lesions of the medial amygdaloid nucleus. However, this behavioral change was also seen in some of the control animals which had been caged for the same period. Psychic blindness was not obtained from any of the structures investigated in this study. Unilateral lesions of the individual nuclei of the amygdaloid complex failed to produce behavioral changes.

Stimulation of the medial amygdaloid area has been shown to produce ovulation and uterine contraction. In this study, bilateral lesions of the lateral nucleus produced permanent hypersexuality. These results suggest an antagonistic influence between the lateral and medial areas.

The behavioral alterations resulting from stimulation and lesion of the amygdaloid nuclei may be a result of altering the normal balance between these two areas.

Indications have been noted which suggest that further localization within the amygdaloid complex is possible.

The assistance of Dr. G. Milton Shy of the National Institute of Neurological Diseases and Blindness and Dr. Eli S. Goldensohn of the New York Neurological Institute in carrying out this research is acknowledged with sincere thanks.

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■ We must be very careful both in ophthalmological and neurological studies not to confound sensations, colours, for an example, which are states of mind, with activities of sensory elements, which are states of body. We must not speak of any mental states as occurring *from*, but as arising *during*, nervous discharges; only physical effects, such as movements, arise *from* nervous discharges. We must also distinguish different degrees of elaborateness of different mental states; "seeing faces" is a greatly more elaborate mental state than colour projections at the onset of an epileptic fit; what I have called the "dreamy state" is vastly more elaborate than "seeing faces." Whilst I think that colour projections at the onset of an epileptic fit arise *during* the epileptic discharge, I believe that so elaborate a state as "seeing faces," and the still more elaborate mental state, the "dreamy state," do not, but that they arise *during* discharges only slightly stronger than normal. The "dreamy state" is a very voluminous mental state; it is commonly called an intellectual aura. As I have implicitly said, I do not believe it to be an aura of warning — not a thing, I mean, of the same meaning as the crude sensations of colour, etc. Admitting that crude sensations arise *during*, and that convulsions occur *from* the epileptic discharge, I urge that elaborate mental states arise *during*, and that movements properly so called occur *from*, but slightly raised discharges of nervous arrangements.

J. Hughlings Jackson in *Ophthalmology and Diseases of the Nervous System*, published in 1886.

A study of cholinesterase and ali-esterase in various neurologic diseases

Joseph Bernsohn, Ph.D., Benjamin Boshes, M.D., Ph.D. and Leroy Possley, M.S.

THE PRESENT INVESTIGATION is the first of a series designed to evaluate the activity and significance of various enzyme systems in human cerebrospinal fluid. Implicit in this study is the assumption that, except for pathologic states wherein a breakdown in the blood-brain barrier occurs, the enzymic activity of the cerebrospinal fluid is a reflection of the enzymologic situation existing in the central nervous tissue. Where the blood-brain barrier is not performing its normal function, the contribution by plasma and erythrocytes to the activity of the cerebrospinal fluid may be at a level that precludes any interpretation of the significance of the enzymatic activity. This is certainly true of the cholinesterases where the blood cholinesterase/cerebrospinal fluid cholinesterase ratio is approximately 200:1.[1]

Cholinesterases in cerebrospinal fluid have been studied previously.[2–5] While the distinction between the true and pseudo-cholinesterase has generally been recognized, the two enzymes have been measured using specific but nonphysiologic substrates, usually acetyl-beta-methylcholine (Mecholyl) for the assay of true cholinesterase and benzoylcholine for measurement of the pseudo-cholinesterase. Since acetylcholine/Mecholyl and acetylcholine/benzoylcholine ratios have been established,[2] these technics may be quite valid. However, it seemed that measurements of both enzymes by acetylcholine hydrolysis would more nearly reflect the physiologic situation, even though the substrate of pseudo-cholinesterase in vivo is still problematic. In addition, the enzymatic activity using these nonphysiologic substrates is considerably less than that for acetylcholine, rendering the methods relatively less sensitive. To obviate these difficulties, the hydrolysis of acetylcholine was measured in the absence and in the presence of Mytelase (N', N',-bis-(2-diethylaminoethyl) oxamide bis-2-chlorobenzyl chloride), which is a specific true cholinesterase inhibitor.

The role of ali-esterase in physiologic function is obscure, but the presence of an active esterase in blood and in other tissues has been demonstrated.[6] Glasson and Mutrux[7] reported the presence of a small amount of ali-esterase in spinal fluid, whereas Kalsbeek, Cohen, and Bovens[1] were unable to find any cerebrospinal fluid ali-esterase activity. However, ali-esterase is an ill-defined enzyme and its activity is dependent on the substrate employed. This laboratory has utilized phenyl acetate to measure ali-esterase activity, and this ester has been found to be readily hydrolyzed by most tissues at a rapid rate. Since the compound is also a substrate for true cholinesterase, eserine at 5×10^{-5}M has been employed to block this enzyme. This concentration of eserine inhibits cholinesterase completely, but has only a slight effect on ali-esterase activity.

MATERIALS AND METHODS

Cerebrospinal fluid was obtained by lumbar puncture from 159 patients, chiefly adult males with a wide spectrum of neurologic disorders. The fluid was stored at 4°C. until ready for assay. Under these conditions, the enzymes have been found to be stable for a month or two.[8] Total protein was determined by the Folin-Ciocalteu method,[9] and a factor of 16 used to convert tyrosine equivalents to protein.

Esterase activity was obtained by manometric measurements in the conventional Warburg apparatus, by a modification of the method of

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Ammon.[10] Determinations were made in duplicate and corrected for nonenzymatic hydrolysis. For the cholinesterase estimations, 1 ml. of cerebrospinal fluid was pipetted into the main compartment, which contained 0.4 to 0.5 ml. of 0.023 M bicarbonate-0.154 M NaCl buffer. Total cholinesterase activity was obtained by tipping in from the side-arm 0.5 ml. of .012 M acetylcholine in the buffer to provide a final substrate concentration of .003 M. Another determination was made with an identical reaction mixture, plus the addition of 0.1 ml. Mytelase in the buffer to yield a final concentration of $1x10^{-7}$M of the inhibitor. This gave the pseudo-cholinesterase activity which, subtracted from the total cholinesterase activity, was a measurement of true cholinesterase. It is realized that the pseudo-cholinesterase determination was not made at the optimal substrate concentration of that enzyme, but, since only one concentration of acetylcholine is present in the cerebrospinal fluid at any particular time, it was believed that this procedure mirrored the physiologic situation more closely than that of obtaining maximum activity under different substrate concentrations, which would have more validity from an enzymologic point of view.

Ali-esterase activity was determined by measuring the rate of hydrolysis of phenyl acetate at a final concentration of $2x10^{-2}$M. Ca^{++}(.001M) was added to the bicarbonate-saline buffer, as this ion has been shown to be a co-factor in ali-esterase activity.[11] To prevent hydrolysis of the substrate by cholinesterases, eserine in a final concentration of $5x10^{-5}$M was added to the main compartment. The volume of cerebrospinal fluid used varied between 0.1 and 0.5 ml., depending on the ali-esterase activity.

All vessels were gassed with 95 per cent N_2-5 per cent CO_2 and assays were carried out at 37°C. for a period of 60 minutes. Values were calculated on the basis of initial velocity, but essentially the reaction rate simulated a zero-order reaction over the whole experimental period. The final volume for all assays was 2.0 ml. Results are expressed both as micromoles of substrate hydrolyzed/100 ml. cerebrospinal fluid/hour, and also micromoles/mg. cerebrospinal fluid protein/hour.

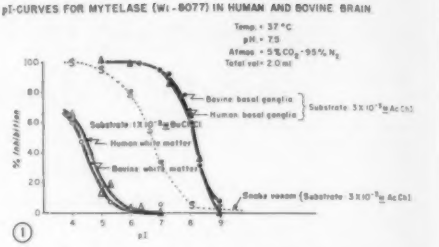

FIG. 1. Inhibitory effect of Mytelase on true and pseudo-cholinesterase in human and bovine brain.

RESULTS

The inhibitory effect of Mytelase on true and pseudo-cholinesterase using human blood as an enzyme source is shown in figure 1. The percentage of inhibition is plotted against pI, which is the reciprocal of the logarithm of the inhibitor concentration. For the true cholinesterase obtained from erythrocytes, and with acetylcholine as a substrate, it can be seen that, at a Mytelase concentration greater than 10^{-7}M, complete inhibition of the enzyme occurs. Using human serum as a source of pseudo-cholinesterase, the effect of the inhibitor on this enzyme with three different substrates was tested. With benzoylcholine, no inhibition with Mytelase occurred below a concentration of 10^{-5}M. Butyrylcholine and acetylcholine were almost similarly inhibited over a range of Mytelase concentrations studied, with the latter showing a somewhat greater degree of sensitivity. It can be seen that, at 10^{-7}M Mytelase, where complete inhibition of the true cholinesterase occurs, practically no inhibition of any of the three substrates employed for pseudo-cholinesterase measurement is evident. Therefore, this concentration of mytelase was used in our work to differentiate the two enzymes.

The results obtained in six neuropathologic categories, with the number of cases studied indicated, are presented in tables 1, 2 and 3. In the absence of any values from a normal control group, only the differences obtained between any of the pathologic conditions can be pointed out.

TRUE CHOLINESTERASE

The results obtained on the activity of true cholinesterase activity in spinal fluid, as well as that of the other two enzymes studied, revealed a wide range of activity within the

TABLE 1

TRUE CHOLINESTERASE ACTIVITY OF CEREBROSPINAL FLUIDS IN NEUROPATHOLOGIC STATES

Activity = micromoles/hour

Diagnosis	*Per 100 ml. CSF*	*Per mg. CSF Protein*
Multiple sclerosis (15)	60.9 (22-130)	1.28 (0.28-2.64)
Hemiplegia after CVA (24)	55.4 (7-120)	1.08 (0.10-2.43)
Epilepsy: idiopathic (13)	62.4 (14-112)	1.35 (0.26-3.39)
Epilepsy: organic (7)	70.7 (43-136)	1.76 (0.94-3.30)
Guillain-Barré (4)	42.3 (11-76)	0.26 (0.03-0.60)
Myasthenia gravis (7)	126.6 (58-250)	3.81 (0.79-8.63)

groups (table 1). What the range of activity for these enzymes might be in a normal population is problematic, but results obtained by other workers have shown the same wide range, as evidenced in this study. Whether low or high values within the groups could be correlated with the severity of pathology or with a remissive or exacerbated phase of the disease was not determined.

The significant finding for true cholinesterase was in the observation that seven cases of myasthenia gravis had true cholinesterase activities, averaging 126.6 micro-moles/100 ml. of cerebrospinal fluid/hour, as compared to a mean of 60.9 for multiple sclerosis, 55.4 for the hemiplegia following a cerebrovascular accident, 62.4 and 70.7 for idiopathic and organic epilepsy, respectively, and 42.3 for four patients with Guillain-Barré syndrome.

When the results are expressed on a per mg. cerebrospinal fluid protein basis, they are even more striking, since the protein content of cerebrospinal fluid in myasthenia gravis averaged 29.5 mg. per cent, which was lower than the value of the other groups. The average of 3.81 micromoles/mg. protein/hour was 200 to 300 per cent higher than the value obtained in multiple sclerosis, hemiplegia, or epilepsy.

The results obtained in Guillian-Barré syndrome showed a low true cholinesterase activity when this was expressed in terms of mg. of cerebrospinal fluid protein, which is high in this pathologic process.

PSEUDO-CHOLINESTERASE

The pseudo-cholinesterase activity showed no remarkable deviations from group to group, except in those with the Guillain-Barré syndrome (table 2). Here the activity of the enzyme was considerably higher than in the other categories, but, when expressed per mg. of cerebrospinal fluid protein, the average was considerably lowered. Evidently only a minor part of the increased protein in the cerebrospinal fluid in this syndrome is associated with pseudo-cholinesterase activity. It is also of some interest that four of the cerebrospinal fluids tested showed a pseudo-cholinesterase activity which was not measurable. Again, as noted for true cholinesterase, the range of values was considerable.

The ratio of pseudo-cholinesterase/true cholinesterase averaged 0.60 for multiple sclerosis, 0.47 for hemiplegias, 0.47 in epilepsy, 1.88 in Guillain-Barré syndrome, and 0.26 in myasthenia gravis. Thus it can be seen that the activity of true cholinesterase toward acetylcholine is two or three times the activity of the pseudo-cholinesterase for the same substrate. In myasthenia gravis this ratio is almost 4:1, due largely to the increased activity of true cholinesterase, and in the Gullain-Barré syndrome pseudo-cholinesterase activity is higher than true cholinesterase activity, the ratio being 1.88:1. These are averages, and in each group with the exception of the last two, there were isolated cases of an inverted ratio.

TABLE 2

PSEUDO-CHOLINESTERASE ACTIVITY OF CEREBROSPINAL FLUID IN NEUROPATHOLOGIC STATES

Activity = micromoles/hour

Diagnosis	*Per 100 ml. CSF*	*Per mg. CSF Protein*	*P/T*
Multiple sclerosis (15)	42.5 (6.7-76)	0.76 (0.17-1.65)	0.60
Hemiplegia after CVA (24)	29.9 (0-69)	0.51 (0-1.32)	0.47
Epilepsy: idiopathic (13)	33.5 (0-715)	0.64 (0-1.45)	0.47
Epilepsy: organic (7)	30.8 (0-69)	0.68 (0-1.38)	0.39
Guillain-Barré (4)	98.3 (11-163)	0.49 (0.05-1.0)	1.88
Myasthenia gravis (7)	32.2 (18-65)	1.01 (0.05-2.24)	0.26

TABLE 3

ALI-ESTERASE ACTIVITY OF CEREBROSPINAL FLUID IN NEUROPATHOLOGIC STATES

Activity = micromoles/hour

Diagnosis	*Per 100 ml. CSF*	*Per mg. CSF Protein*
Multiple sclerosis (15)	1011 (196-2800)	18.2 (4.2-42.0)
Hemiplegia after CVA (24)	1264 (208-3660)	21.7 (6.2-43.8)
Epilepsy: idiopathic (13)	1455 (384-3500)	27.8 (7.0-81.4)
Epilepsy: organic (7)	635 (268-866)	15.5 (5.8-26.4)
Guillain-Barré (4)	10,660 (3970-18,850)	44.7 (20-61)
Myasthenia gravis (7)	789 (392-2101)	18.0 (7-29.5)

ALI-ESTERASE

It is obvious that an active ali-esterase system is present in cerebrospinal fluid, if phenyl acetate is used as a substrate (table 3). The lowest ali-esterase activity found in one case of multiple sclerosis was 196 micro-moles of substrate hydrolyzed/100 ml. of cerebrospinal fluid/hour, and was comparable to the highest range of cholinesterase activity. The value of approximately 1000 micro-moles/100 ml. of cerebrospinal fluid/hour is about 1/750 of the activity in blood.[6] The outstanding finding was the extraordinarily high activity in the Guillain-Barré syndrome, averaging 10,660 micro-moles for the four cases. However, when this activity was expressed on a mg. per cent protein basis, the value of 44.7 was only moderately in excess of that found in the other groups. This would indicate that the increase in activity is associated with the increase in protein in the cerebrospinal fluid.

Of additional interest are the results obtained in epilepsy. When patients with the idopathic form are compared to those due to organic causes, a difference in the ali-esterase activity of the spinal fluid is apparent. Despite some degree of overlapping, the former have a higher ali-esterase activity than the latter, 27.8: 15.5. Except for the Guillain-Barré group, which offers an exceptional case because of the high albumin content in the cerebrospinal fluid, the idiopathic epilepsy fluids have a higher ali-esterase activity than the other categories, averaging 1,455 micro-moles per 100 ml./hour, whereas the organic group has the lowest activity, 635 micro-moles/100 ml./hour. While the lower activity in the latter may be of questionable significance, the high activity in the epileptics with no organic etiology bears further investigation.

The results obtained for enzymatic activity in a number of other neuropathologic conditions are shown in tables 4, 5, and 6. No remarkable differences are apparent from the averages found in multiple sclerosis and hemiplegia, with some exceptions as follows: 1) a high ali-esterase activity in one case each of meningoencephalitis and toxic encephalopathy and residual of acute poliomyelitis; 2) a high true cholinesterase value expressed on a per mg. cerebrospinal fluid protein basis in one case of porphyrinuria, and a high value in one case of cortical atrophy expressed per 100 ml. of cerebrospinal fluid. The wide range of activity for the three enzymes is apparent.

DISCUSSION

It would be of interest to correlate enzymatic activity with pathologic processes in central nervous tissue. The role of true cholinesterase in the bioelectric phenomena associated with the propagation of the nerve impulse has undergone intensive investigation. It seems also that this enzyme is localized in neuronal elements and ganglia.[12,13] Thus, pathologic proc-

TABLE 4

CHOLINESTERASES AND ALI-ESTERASE IN CSF IN NEUROPATHOLOGIC STATES

Activity = Micromoles/hour/mg. CSF Protein

Diagnosis	*True Cholinesterase*	*Pseudo-Cholinesterase*	*Ali-Esterase*
Porphyrinuria	4.6	2.1	20.3
Meningoencephalomyelitis	0.4	0.67	66.6
Cortical atrophy	2.77	1.00	33.6
Ulnar nerve palsy	1.61	0.0	21.1
Myelopathy—C-7	1.04	2.33	16.8
Metastatic brain tumor	0.53	0.24	13.4

TABLE 5

CHOLINESTERASES AND ALI-ESTERASE IN CSF IN NEUROPATHOLOGIC STATES

Activity = Micromoles/hour/mg. CSF Protein

Diagnosis	*True Cholinesterase*	*Pseudo-Cholinesterase*	*Ali-Esterase*
Syphilis	0.19	0.26	7.6
Neurosyphilis	1.56	0.47	3.8
General paresis	0.68	0.00	4.4
Spinal cord tumor	1.96	0.64	35.2
Amyotrophic lateral sclerosis	0.70	0.64	10.7
Paralysis agitans	0.88	1.78	23.2

esses involving destruction of gray matter might conceivably contribute to a true cholinesterase increase in cerebrospinal fluid in a manner analogous to transaminase accretion after destruction of nervous tissue due to experimental cerebral artery occlusion.[14]

Increases in this enzyme could be demonstrated in seven cases of myasthenia gravis, one of cortical atrophy, and one of porphyrinuria. Results in the last two cases substantiate the thesis of increase after parenchymal destruction, but in two cases of general paresis no increase in enzymatic activity was noted. Of significance is the increase in activity observed in myasthenia gravis. Should a more extensive study confirm this finding, the metabolic derangement hitherto implicit in this disease would have verification. Studies on blood and other tissues in this syndrome[15] have failed to demonstrate any abnormal true cholinesterase activity. Thus, while other explanations, such as decreased acetylcholine synthesis or deficient activity at the myoneural junction, have been advanced as the etiologic factor in myasthenia gravis, the results obtained here would implicate an increased true cholinesterase activity which presumably leads to the prevention of adequate amounts of acetylcholine being localized at the synaptic junction.

Pseudo-cholinesterase function is essentially unknown, though it may serve as a safety factor in acetylcholine hydrolysis. The enzyme is localized in the walls of blood vessels and in glial tissue and Schwann cells.[16] The site of localization has led to postulates that the enzyme may be involved in the demyelinating process.[17] However, there is no evidence that the cerebrospinal fluid levels of pseudocholinesterase in multiple sclerosis differ from non-demyelinating diseases. The enzyme may be a factor in processes responsible for maintaining myelin integrity, since demyelination may proceed at a rate not compatible with measurable changes in pseudo-cholinesterase in the cerebrospinal fluid.

It should be noted that inverse true/pseudo-cholinesterase ratios appear (in the Guillain-Barré syndrome, for example). Increases in this enzyme have been correlated with increases in cerebrospinal fluid protein,[18] but there are exceptions to this concept. Since the pseudo-cholinesterase is associated with the alpha-2-globulin,[19] no increase in this enzyme will occur unless this fraction is part of the protein increment. It will require more fundamental data before such correlations can be evaluated.

The role of ali-esterase in neurologic processes is more difficult to evaluate. These data indicate that cerebrospinal fluid has significant ali-esterase activity, contrary to the finding of Kalsbeek and co-workers.[1] As pointed out earlier, ali-esterase activity must be correlated

TABLE 6

CHOLINESTERASES AND ALI-ESTERASE IN CSF IN NEUROPATHOLOGIC STATES

Activity = Micromoles/hour/mg. CSF Protein

Diagnosis	*True Cholinesterase*	*Pseudo-Cholinesterase*	*Ali-Esterase*
Myotonia congenita	0.49	0.24	4.9
Toxic encephalopathy	0.02	0.71	74.5
Herniated nucleus	1.31	1.06	65.8
Cerebellar ataxia	1.13	0.21	33.3
Poliomyelitis (residual)	0.32	0.44	48.3
Diabetic neuropathy	1.16	0.24	8.0
Wilson's disease	0.18	0.12	20.6

with the substrate employed to measure this enzyme. However, examination of the data of Kalsbeek shows that, with at least one of the substrates used to measure ali-esterase activity, namely, methyl butyrate, considerable hydrolysis occurred in four of the five pooled cerebrospinal fluid samples used in that study.

One of the older theories of the etiology of multiple sclerosis on a biochemical level was concerned with a myelinolytic agent responsible for myelin degradation.[20] This concept of Marburg was enlarged by Brickner[21] to involve esterases, and presumably the ali-esterase measured here might be a component of that group. The results in multiple sclerosis in this study, however, do not show any abnormal esterase activity.

The increase found in the Guillain-Barré syndrome is of interest because high ali-esterase activity is observed. This can be expected, in view of the fact that the protein increment in this syndrome is albumin in character and the enzyme has been found to be in the albumin fraction in serum.[22]

SUMMARY

1. The true-cholinesterase, pseudo-cholinesterase, and ali-esterase activities of cerebrospinal fluid in 159 patients with various neuropathologic conditions were determined. The two cholinesterases were estimated by their activity on the same substrate, acetylcholine, and differentiated by the use of Mytelase, a specific true-cholinesterase inhibitor.

2. In the studies in multiple sclerosis, hemiplegia after cerebrovascular accident, epilepsy, myasthenia gravis, and Guillain-Barré syndrome, a wide range of activity was evident for the three enzymes studied. Cerebrospinal fluid was found to contain an active ali-esterase, using phenyl acetate as a substrate.

3. A high true-cholinesterase activity was found in seven cases of myasthenia gravis, one of cortical atrophy, and one of porphyrinuria.

4. No evidence of any deviation in pseudocholinesterase or ali-esterase activity was evident in the spinal fluid in multiple sclerosis.

5. A difference in ali-esterase activity in cases of epilepsy from organic causes as compared to the idiopathic form was observed.

6. A high ali-esterase activity was found in the Guillain-Barré syndrome, which was correlated with the high albumin fraction in cerebrospinal fluid.

We are indebted to the Winthrop Laboratories for supplying Mytelase (Win-8077).

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PROGRAM OF THE
AMERICAN ACADEMY OF NEUROLOGY

Tenth Annual Meeting

April 21 – 26, 1958

Bellevue-Stratford Hotel — *Philadelphia, Pennsylvania*

GENERAL SCIENTIFIC PROGRAM

Review Courses in Basic and Clinical Neurology

April 21, 22, 23, 1958

Intensive review courses in basic and clinical neurology will be offered preceding the annual meeting, sponsored and arranged by the American Academy of Neurology. Courses will be held as follows:

Neuropathology—April 21, 1958

Disorders of Movement—April 21, 1958

Neuropharmacology—April 21, 1958

Electroencephalography—April 22, 1958

Pediatric Neurology—April 22, 1958

Physiology and Diseases of Cerebral Circulation—April 22, 1958

Current Advances in Neurology—April 23, 1958

Neuro-ophthalmology—April 23, 1958

Fine Structure of the Nervous System — April 23, 1958

Additional information regarding these courses may be obtained from Mrs. J. C. McKinley, Executive Secretary, 3501 East 54th Street, Minneapolis 17, Minnesota. No application will be accepted after April 1, 1958.

Important Notice Regarding Scientific Sessions

This year the general scientific program will be held in five sessions, each separate, on Thursday morning, April 24, Friday morning and afternoon, April 25, and Saturday morning and afternoon, April 26. Business meetings of the Academy will be held at 5:00 p.m. on April 24 and 25.

There are now three special sections with concurrent meetings. The Section of Neurochemistry will meet Thursday afternoon, April 24 and Friday morning, April 25. The Section of Neuroanatomic Sciences will meet Thursday afternoon, April 24 and Friday morning, April 25. The Section of Neuropharmacology will meet only on Thursday afternoon, April 24.

The programs for these meetings are listed separately.

THURSDAY, APRIL 24, 1958

Morning Session 9:00 a.m.

Chairman: John Sullivan, *Boston, Massachusetts*

Secretary: Sherwood Davidson, *Boston, Massachusetts*

Junior Prize Essay
Subject and author to be announced. This is the annual prize awarded by the Woman's Auxiliary to the American Academy of Neurology to the junior member who submitted the manuscript adjudged best by the prize committee.

The Pathologic Basis of Chorea and Choreoathetosis (Robert Wartenberg Memorial Lecture)
J. Godwin Greenfield, *London, England*

Experimental Dyskinesia in the Rhesus Monkey
Malcolm B. Carpenter, *New York City*

Neurophysiologic Aspects of Congenital Bilateral Athetosis
Thomas E. Twitchell, *Boston, Massachusetts*

Akinesia in Parkinson's Disease
Robert S. Schwab, Albert C. England, Jr. and Elizabeth Peterson, *Boston, Massachusetts*

Reserpine in Chronic Progressive (Huntington's) Chorea
Warren H. Kempinsky, William R. Boniface, Peter P. Morgan and Anthony K. Busch, *St. Louis, Missouri*

A Five-Year Follow-up Study of Clinical Results and Neurophysiologic Aspects of 600 Globus Pallidus and Thalamic Operations for Parkinsonism
Irving S. Cooper, *New York City*

Pneumotaxic Localization, Recording, Stimulation and Section of the Basal Structures of the Brain in Dyskinesias
C. Bertrand, L. Poirier, N. Martinez and C. Gauthier, *Montreal, Quebec, Canada*

Long-Range Effects of Pallido-Ansotomy in Extrapyramidal and Convulsive Disorders
E. A. Spiegel, H. T. Wycis and H. W. Baird, III, *Philadelphia, Pennsylvania*

A Simple Percutaneous Method for the Implantation of Electrodes and/or Cannulae in the Brain
John C. Lilly, *Bethesda, Maryland*

A Myographic Study of Reflex Movement and the Abnormal Tonal State
Leroy Kurth, Donald Higgins and Louis P. Sanchez-Longo, *Washington, D.C.*

Electro-oculographic Investigation of Vestibular Responses in Normal Subjects and in Patients with Intracranial Disease
Paul J. Anderson, Sidney P. Diamond, Philip S. Bergman and Morton Nathanson, *New York City*

THURSDAY, APRIL 24, 1958

Afternoon Sessions: Meetings of Sections of Neurochemistry, Neuropharmacology, and Neuroanatomical Sciences (separate programs listed below).

Business Meeting 5:00 p.m.
Francis M. Forster, presiding

THURSDAY, APRIL 24, 1958

Evening Session 8:00 p.m.
Chairman: Ward C. Halstead, *Chicago, Illinois*

A RESEARCH SYMPOSIUM

Higher Brain Functions
The following topics will be considered:

Neural Mechanisms and Memory
Ronald Myers, *Washington, D.C.*

Neural Mechanisms and Perception
Austin Riesen, *Chicago, Illinois*

Neural Mechanisms and Thinking
Ralph Reitan, *Indianapolis, Indiana*

Discussion to be opened by Morris B. Bender, *New York City*

FRIDAY, APRIL 25, 1958

Morning Session 9:00 a.m.

Chairman: George D. Gammon, *Philadelphia, Pennsylvania*

Secretary: William W. Wilson, *Philadelphia, Pennsylvania*

Menstruation and Epilepsy: The Role of Estrogen in Catamenial Seizures
John Logothetis, Richard Harner, Frank Morrell and Fernando Torres, *Minneapolis, Minnesota*

The Influence of Adrenal Function on the Treatment of Epilepsy
Patrick F. Bray, Gerardo Zapata, Robert S. Ely and Vincent C. Kelley, *Salt Lake City, Utah*

Treatment of Light-Sensitive Epilepsy
C. Wesley Watson, John Hunter, Reinette Bowker and Elliott Marcus, *Boston, Massachusetts*

Mechanism of Convulsive Seizures Induced by Pyridoxine Deficiency
Robert Kamrin and George D. Gammon, *Philadelphia, Pennsylvania*

Production of Injury to the Central Nervous System with a Nucleic Acid Antimetabolite
Harold Koenig, *Chicago, Illinois*

Synaptic Mechanisms Involved in Activation of Corticospinal Neurons
Dominick P. Purpura, Martin Girado and Harry Grundfest, *New York City*

Formation of Gamma-aminobutyric Acid (GABA) from Glutamic Acid in Vivo
Eugene Roberts and Claude F. Baxter, *Duarte, California*

Serum Magnesium in Delirium Tremens and Alcoholic Hallucinosis
Jack Mendelson, Donald Wexler, P. Herbert Leiderman and Philip Solomon, *Boston, Massachusetts*

Use of Oximes in the Management of Neuromuscular Block due to Anticholinesterase Compounds in Normal Subjects and Patients with Myasthenia Gravis
D. Grob and R. J. Johns, *Baltimore, Maryland*

Patterns of Facilitation and Inhibition in Myasthenic Muscle
Daniel S. Feldman and Irving H. Wagman, *New York City*

Quantitative Determination of Porphyrins in the Central and Peripheral Nervous System
Frank H. J. Figge and Harvey M. Solomon, *Baltimore, Maryland*

Therapy of Acute Porphyria with Chelating and Other Agents
Henry A. Peters, *Madison, Wisconsin*

Glutamic Oxalacetic Transaminase (GOT) and Lactic Dehydrogenase (LDH) Activities in the Cerebrospinal Fluid of Brain Tumor Patients, in Normal Human Brain, and in Brain Tumors
Joseph B. Green, Henry A. Oldewurtel and Francis M. Forster, *Washington, D.C.*

Paroxysmal Paralytic Myoglobinuria
Julius Korein, David R. Coddon and Frederick H. Mowrey, *Parks Air Force Base, California*

FRIDAY, APRIL 25, 1958

Morning Session Meetings of Sections of Neurochemistry and Neuroanatomical Sciences (separate programs listed below).

FRIDAY, APRIL 25, 1958

Afternoon Session 2:00 p.m.

Chairman: Benjamin Boshes, *Chicago, Illinois*
Secretary: Joel Brumlik, *Chicago, Illinois*

Cluster Headaches
Arnold P. Friedman, H. Mikropoulos and C. Enker, *New York City*

Evidence for a Proteolytic Enzyme in Cerebrospinal Fluid during Vascular Headache of the Migraine Type
Loring F. Chapman and Harold G. Wolff, *New York City*

Promising Results in Cryptococcal Meningitis
Harry Rubin and Michael L. Furcolow, *Kansas City, Kansas*

Central Pontine Myelinolysis
Raymond D. Adams, Maurice Victor and Elliott L. Mancall, *Boston, Massachusetts*

The Carcinomatous Neuromyopathies
Sir Russell Brain, *London, England*

Studies on the Cerebral Pacemaker
R. B. Aird and B. Garoutte, *San Francisco, California*

A New Model for Human Psychologic Processes
Lawrence S. Kubie, *New York City*

Millipore Filter Tubulation used to Regenerate Gaps in Adult Feline Sciatic Nerves
Jakob Husby, C. A. L. Bassett, C. R. Noback and J. B. Campbell, *New York City*

The Use of Peripheral Nerve Spinal Cord Anastomosis for Surgical Treatment of Experimental Spinal Cord Transection in the Dog
C. C. Turbes and L. W. Freeman, *Bloomington, Indiana*

Conduction Velocity of the Motor Fibers of Peripheral Nerves in Peroneal Muscular Atrophy
E. H. Lambert, J. A. Bastron and D. W. Mulder, *Rochester, Minnesota*

Business Meeting 5:00 p.m.

Francis M. Forster, presiding

SATURDAY, APRIL 26, 1958

Morning Session 9:00 a.m.

Chairman: Clark H. Millikan, *Rochester, Minnesota*

Secretary: James A. Bastron, *Rochester, Minnesota*

Problems of Cerebral Blood Supply
Bernard J. Alpers, *Philadelphia, Pennsylvania*

The Prognosis of Some Brainstem Vascular Syndromes
Robert D. Currier, Conrad L. Giles and Martha R. Westerberg, *Ann Arbor, Michigan*

The Very Hemorrhagic Infarct
John B. Baker and Walter A. Olszewski, *Boston, Massachusetts*

Localized Cerebral Hypoglycemia Simulating Apoplexy. A Clinical and Experimental Study
John S. Meyer and Harold Portnoy, *Detroit, Michigan*

Intermittent Carotid and Vertebral Basilar Insufficiency Associated with Polycythemia
C. H. Millikan, R. G. Siekert and J. P. Whisnant, *Rochester, Minnesota*

Neurologic Complications of Coarctation of the Aorta
H. Richard Tyler and David B. Clark, *Boston, Massachusetts* and *Baltimore, Maryland*

Carotid Occlusion in Treatment of Cerebral Vascular Disease
William H. Sweet, Hannibal Hamlin, Jost J. Michelsen and Federico Mora, *Boston, Massachusetts*

The Surgical Treatment of Patients with Arteriosclerotic Cerebrovascular Accidents
William S. Fields and E. Stanley Crawford, *Houston, Texas*

Effects of Bilateral Cerebral Infarction on Respiratory Center Sensitivity and Arterial Blood Gases
R. I. Birchfield, H. O. Sieker and A. Heyman, *Durham, North Carolina*

The Effect on the Electroencephalogram of Differential Regulation of CO_2 and pH
August G. Swanson, L. S. Stavney and Fred Plum, *Seattle, Washington*

A Biochemical Study of the Cerebrospinal Fluid at Various Times after Subarachnoid Hemorrhage
Wallace W. Tourtellotte, H. Itabashi, Beverley A. Skrentny and Russell N. DeJong, *Ann Arbor, Michigan*

Spinal Epidural Hematoma: A Complication of Anticoagulant Therapy
Simon Horenstein, Bertram Winer and Albert Starr, *Boston, Massachusetts*

The Neurologic Effects of Barbiturates Given via Intracarotid Catheters in the Cat
Murray E. Jarvik and Alan B. Rothballer, *New York City*

SATURDAY, APRIL 26, 1958

Afternoon Session 2:00 p.m.

Chairman: Desmond S. O'Doherty, *Washington, D.C.*

Secretary: Joseph B. Green, *Washington, D.C.*

X-Ray Radiation Encephalopathy
J. H. Sung, David Cowen and Abner Wolf, *New York City*

On the Chemical Basis of the Marchi Method for Degenerating Myelin
Frederick Wolfgram and Augustus S. Rose, *Los Angeles, California*

A Study of Senile Cerebral Changes with Newer Staining Techniques
George Margolis, *Durham, North Carolina*

The Syndrome of Progressive Cerebral Degeneration in Infancy and Childhood
Harold Stevens and Anatole Dekaban, *Washington, D.C.*

Chronic Relapsing Inclusion Encephalitis with Eight and One-Half Year Survival
William M. Landau and Sarah A. Luse, *St. Louis, Missouri*

Optic Neuritis in Children
Charles Kennedy, Frank D. Carroll and Sidney Carter, *New York City*

The Genesis of Distended Central Nervous System, Hydrocephalus and Cranioschisis in the Mouse Embryo
Theodore H. Ingalls and Ujihiro Murakami, *Boston, Massachusetts*

Effects of Brainstem Lesions on Cortically Induced Motor Phenomena
S. Shanzer, I. H. Wagman, C. A. Papatheodorou and M. B. Bender, *New York City*

Diencephalic and Mesencephalic Influence on Limbic System Seizures in the Cat
O. J. Andy, M. Allen and R. McC. Chinn, *Jackson, Mississippi*

Early Projection of Large Muscle Afferents from Forelimb of Cat to Somatosensory Cortex
Louis Berlin and Vahe E. Amassian, *New York City*

Pantopaque Myeloencephalogram
Robert Mones and Robert Werman, *New York City*

Association of Skeletal Abnormalities with Motor System Disease
Leonard T. Kurland and Ntinos C. Myrianthopoulos, *Bethesda, Maryland*

SECTION OF NEUROPHARMACOLOGY

THURSDAY, APRIL 24, 1958

Afternoon Session 2:00 p.m.

SYMPOSIUM: Pharmacologic Stimulation of the Central Nervous System

Chairman: J. E. P. Toman, *Chicago, Illinois*

Problems of Classification of Central Stimulants
J. E. P. Toman, *Chicago, Illinois*

Antidepressives
Nathan S. Kline and John C. Saunders, *Orangeburg, New York*

Electroencephalographic Studies of Drug Effects
Douglas Goldman, *Cincinnati, Ohio*

Self-Injection Experiments
James J. Olds, *Ann Arbor, Michigan*

Hallucinatory Effects in Man of Acetylcholine Inhibitors
Carl C. Pfeiffer, *Atlanta, Georgia*

Analeptics
R. K. Richards, *Chicago, Illinois*

The Multiplicity of Factors in Drug Stimulation of the Nervous System
Chauncey C. Leake, *Columbus, Ohio*

Following the symposium there will be a brief business meeting of the Neuropharmacology Section.

Neuropharmacology will meet jointly with Neurochemistry on Friday, April 25 (see program).

SECTION OF NEUROCHEMISTRY

THURSDAY, APRIL 24, 1958

Afternoon Session 1:00 p.m.

SYMPOSIUM ON NEUROCHEMISTRY OF NUCLEOTIDES

Moderator: Morris Friedkin, *St. Louis, Missouri*

Secretary: Guy McKhann, *Bethesda, Maryland*

Adenine Nucleotides
Giulio Cantoni, *Bethesda, Maryland*

Guanidine Nucleotides
D. Rao Sanadi, *Berkeley, California*

Cytidine Nucleotides
Roger J. Rossiter, *London, Ontario*
Bernard W. Agranoff, *Bethesda, Maryland*

Uridine Nucleotides
Robert M. Burton, *St. Louis, Missouri*

Pyridine Nucleotides
Nathan Kaplan, *Boston, Massachusetts*

Polynucleotides
Dan Bradley, *Bethesda, Maryland*

FRIDAY, APRIL 25, 1958

Morning Session 9:00 a.m.

SYMPOSIUM ON NEUROCHEMISTRY OF AMINO ACIDS

Moderator: Eugene Roberts, *Duarte, California*

Secretary: Guy McKhann, *Bethesda, Maryland*

Aromatic Amino Acids
Sidney Udenfriend, *Bethesda, Maryland*

Gamma-Aminobutyric Acid
Wayne Albers, *Bethesda, Maryland*
Claude Baxter, *Duarte, California*

Phosphatide Bases
David M. Greenberg, *Berkeley, California*

Glutamine and Asparagine
Donald B. Tower, *Bethesda, Maryland*

Protein Synthesis and Turnover
Heinrich Waelsch, *New York City*

SECTION OF NEUROANATOMIC SCIENCES

THURSDAY, APRIL 24, 1958

Afternoon Session 1:00 p.m.

Chairman: Alphonse R. Vonderahe, *Cincinnati, Ohio*

Neurohistology of Two Mammalian Mutations of Neurological Interest
F. D. Anderson and Pinckney J. Harman, *Jersey City, New Jersey*

Incorporation of Labeled Precursors into Deoxypentose Nucleic Acid (DNA) of Glia in the Mature Mammalian Neuraxis
Harold Koenig, *Chicago, Illinois*

The Millipore Tabulation Technic of Neural Regeneration: An Assay of Bio-Mechanical Factors
C. A. L. Bassett, Jakob Husby, C. R. Noback and J. B. Campbell, *New York City*

Regeneration of Axons in the Adult Mammalian Spinal Cord
Charles R. Noback, C. Andrew L. Bassett, Jakob Husby and James B. Campbell, *New York City*

Serial Observations of Myelin Formation and Degeneration in Cultures of New-Born Rat and Kitten Cerebellum
Murray B. Bornstein, *New York City*

A Direct Cochleocerebellar Connection
G. L. Rasmussen, *Bethesda, Maryland*

Cerebellar Potentials Evoked by Repetitive Stimulation of the Cerebral Cortex
Alma M. Stoiber, *Chicago, Illinois*

Anatomic Projection of Cerebellar Nuclei to the Brainstem in Cat
James M. Sprague and William W. Chambers, Philadelphia, Pennsylvania

Determination of the Cortical and Thalamic Areas Involved in Taste Discrimination in the Albino Rat
R. M. Benjamin and K. Akert, *Madison, Wisconsin*

A Consideration of the Specificity of the Cerebral Cortical Connections
Berry Campbell, *Minneapolis, Minnesota*

The Fine Structure of the Basal Ganglia
Clement A. Fox, *Milwaukee, Wisconsin*

Further Studies of the Syndrome of Ether Convulsions: The Occurrence of Fat Embolization and its Association with Neurologic Deficits
Guy Owens and H. W. Scott, *Nashville, Tennessee*

Blood-Brain Barrier in the Healing of Cerebral Wounds Studied by Iodinated Bovine Albumin
Jerzy Olszewski and Joseph C. Lee, *Saskatoon, Saskatchewan*

Neuronal Changes in Chronically Reserpinized Monkeys and Cats
William F. Windle and Jan Cammermeyer, *Bethesda, Maryland*

Tremor: Its Inhibition and Production in Cats
W. W. Kaelberg and E. G. Hamel, *Iowa City, Iowa*

Inherited Progressive Retinal Degeneration in C_3H Mice
R. L. Sidman and N. Feder, *Bethesda, Maryland*

FRIDAY, APRIL 25, 1958

Morning Session 9:00 a.m.

SYMPOSIUM ON THE CEREBELLUM

Chairman: Ray S. Snider, *Chicago, Illinois*

Papers to be announced

READ BY TITLE

Generalized Cytomegalic Inclusion Diseases with Severe Cerebral Lesions in the New-Born
Ihsan Sukru Aksel, Talia Bali Aykan and Sami Ucar, *Istanbul, Turkey*

The Effects of Lysergic Acid After Cerebral Ablation
Maitland Baldwin, Shirley A. Lewis and Sven A. Bach, *Bethesda, Maryland*

The Neurologic Complications Following Cardiac Surgery
Lawrence J. Barrows, Howard M. Rawnsley and Harry F. Zinnser, *Philadelphia, Pennsylvania*

Low Spinal Fluid Pressure Syndrome
W. E. Bell and R. J. Joynt, *Iowa City, Iowa*

Clinical Application of a Tactual Formboard Task
Arthur L. Benton and Wayne A. Owen, *Iowa City, Iowa*

The Acute Cerebellar Syndrome of Childhood
M. Blaw and J. Sheehan, *Ann Arbor, Michigan*

Observations on Factors Contributing to Creatinuria in Normal Subjects and Those with Muscular Dystrophy
Nikos Bourdakos and Stewart Wolf, *Oklahoma City, Oklahoma*

Quantitative Chemical and Morphological Studies of Developing Parietal Cortex in the Cat
K. R. Brizzee and Xenia Kharetchko, *Salt Lake City, Utah*

Observations on the Differential Diagnosis Between Early Multiple Sclerosis and Psychoneurosis
Fortunato G. Castillo and Philip Solomon, *Boston, Massachusetts*

Some Effects of 1- (1-Phenylcyclohexyl) Piperidine-HCL on the Monkey
Graham Chen and J. K. Weston, *Detroit, Michigan*

The Relationship of "Little's" Disease to Prematurity
J. A. Churchill, *Detroit, Michigan*

Neurologic Effects of Metal Implants in Cerebral Cortex of Monkeys
Joseph G. Chusid and Lenore M. Kopeloff, *New York City*

A New Diagnostic Technique for Demonstrating Tumors of the Posterior Fossa by the Use of Pantopaque
David R. Coddon, *New York City*

Exercises and Activities for the Parkinson Patient
Lewis J. Doshay, *New York City*

Non-epileptic Seizures
Gregory S. Ferriss, *New Orleans, Louisiana*

Cardiovascular Responses in Man and Dog to Transcranial Electric Stimulation
Lawrence H. Gahagan, Edwin J. de Beer, Kenneth I. Colville, C. H. Ellis, William Hall Lewis, D. Jeanne Richardson and Daniel Sheehan, *Tuckahoe, New York*

Syringomyelia. The Result of Embryonal Atresia of the Fourth Ventricle
W. James Gardner, Jorge Angel, Guy H. Williams and Louis J. Karnosh, *Cleveland, Ohio*

Changes with Age in the Tactual Thresholds of Children
Lila Ghent, *New York City*

Symphosis of the Lateral Ventricles in Marfan's Syndrome
H. W. Gillen, Frank B. Hays and James S. Browne, *Jackson, Mississippi*

Somatic Trigger Point Pain, Referred Pain, Reflex Pain and Sciatica
George S. Hackett, *Canton, Ohio*

Unusual Response of the Inferior Olive to Gliomas
Harris M. Hauser and James W. Kernohan, *Rochester, Minnesota*

Case Report and a Review of the Clinical Aspects of Primary Melanoma of the Central Nervous System
David S. Hays, *Tarrytown, New York*

Production of Labelled Carbon Dioxide by an Excised Sympathetic Ganglion
Paul Horowitz and Martin G. Larrabee, *Baltimore, Maryland*

Neuropsychologic Findings in Children with Dyslexia and Dysgraphia
Hallgrim Klove and Arthur L. Drew, *Indianapolis, Indiana*

A Reevaluation of Lumbar Puncture in the Presence of Papilledema and Intracranial Hypertension
Julius Korein, Humberto Cravioto and Mario Leicach, *New York City*

Role of Stimulus Intensity in Perception of Simultaneous Tactile Stimuli
Hyman Korin and Max Fink, *Glen Oaks, New York*

Acute Cerebellar Ataxia in Childhood
Gene M. Lasater and J. T. Jabbour, *Memphis, Tennessee*

Transverse Myelitis with Herpes Zoster
Gerard M. Lehrer, *New York City*

Tumors of the Central Nervous System in Domestic Animals
John T. McGrath, *Philadelphia, Pennsylvania*

Diagnostic Significance of Routine Skull X-rays in Mentally Defective Patients
William T. McLean, Jr. and Harold M. Manfredi, *Baltimore, Maryland*

Relationship of Disturbances of Weight Discrimination to Other Signs of Parietal Lobe Disease
Ildiko Mohacsy, Erich G. Krueger and Hans-Lukas Teuber, *New York City*

Blood Pressure Mechanisms in Decerebrate and Anesthetized Cats
Roger Merritt Morrell, Staten Island, *New York*

Pneumoencephalography and Its Effects on Serum and Cerebrospinal Fluid Electrolytes
Blaine S. Nashold, William P. Wilson and James Jackson, *Durham, North Carolina*

Impairment of Flicker Discrimination in the Visual Fields of Brain-Damaged Patients
Oscar O. Parsons, *Durham, North Carolina*

Treatment of Tetanus with Intramuscular Meprobamate
M. A. Perlstein, *Chicago, Illionis*

Cutaneous Perception and the "Body Image Concept" in Normal and Abnormal Children
Max Pollack and Edward Gordon, *Brooklyn, New York*

Importance of Pantopaque Ventriculography in the Localization of Expanding and Obstructing Lesions of the Posterior Fossa
Bruce L. Ralston, Sidney W. Gross and Charles Newman, *New York City*

Determination of the Lipides in the Cerebrospinal Fluid
E. Roboz, W. C. Hess, R. R. di Nella and W. Cevallos, *Washington, D. C.*

Evaluation of Megimide as a Convulsant Agent in Clinical Electroencephalography
E. Rodin, *Ann Arbor, Michigan*

Study of the Pathogenesis of Kernicterus
B. Rozdilsky and J. Olszewski, *Saskatoon, Saskatchewan*

In Vitro Myelinolytic Activity of Microflora
L. M. Adelson, G. S. Trelawny and A. Schatz, *Doylestown, Pennsylvania*

Ataxia-Telangiectasia
Robert P. Sedgewick and Elena Boder, *Los Angeles, California*

Effect of Trypan Red and Cortisone in Experimentally Produced Poliomyelitis
Benjamin V. Siegel, William W. Anderson and Robert B. Aird, *San Francisco, California*

Peganone—Effective Anticonvulsant?
Bushnell Smith, *Washington, D. C.*

Metabolism of Organic Boron Compounds in Brain Tumor Patients
Albert H. Soloway, *Boston, Massachusetts*

Diagnosis of Treatment of Cortical and Cerebral Atrophy in Patients under 40
Averill Stowell, *Tulsa, Oklahoma*

Chylomicron Index in Amyotrophic Lateral Sclerosis
Clinton H. Thienes and Ralph G. Skillen, *Pasadena, California*

Win 4692 in the Treatment of Spasticity Produced by Multiple Sclerosis
Fernando Torres, Bernard Sandler and Trudy de Torres, *Minneapolis, Minnesota*

Meningeal Fibroblastoma—A Roentgenologic Study of Skull Vascularity
Sidney P. Traub, *Saskatoon, Saskatchewan*

Isolated Finger Movements in Infantile Spastic Syndromes
Thomas E. Twitchell, *Boston, Massachusetts*

Lactic Dehydrogenase Activity in Cerebrospinal Fluid
H. Richard Tyler, *Boston, Massachusetts*

Clinical and Electroencephalographic Observations in Patients with Muscular Dystrophy
H. L. Wayne and A. N. Browne-Mayers, *New York City*

Lip Sign in Bell's Palsy
E. Y. Williams, *Washington, D. C.*

Electroencephalographic Observations During Experimental Hyperammonemia
W. P. Wilson and M. P. Tyor, *Durham, North Carolina*

The Grape-like Bodies of the Central Nervous System
M. Wolman, *Jerusalem, Israel*

A New Anatomic Concept of Hearing
M. Wharton Young, *Washington, D. C.*

CASE REPORT

Agenesis of the septum pellucidum

William E. Bell, M.D. and Thomas B. Summers, M.D.

THE FIRST reported case of this anomaly appeared in 1880.[1] The patient, a two and one-half year old boy, died of tuberculous meningitis. At postmortem the corpus callosum was intact; however, absence of the septum pellucidum was demonstrated. In 1925 Hochstetter[2] described a case in which there was absence of the septum pellucidum and in which no hydrocephalus or abnormality of the corpus callosum was noted. He stressed the rarity of this abnormality as an isolated finding. In his case there was no record of neurologic disorder clinically. The left optic nerve was found to be partially atrophic; however, Hochstetter felt that this was not related to the absence of the septum pellucidum.

The first case of congenital absence of the septum pellucidum diagnosed by air encephalography was that of Dyke and Davidoff[3] reported in 1935. The patient was a 23 year old female who had suffered from epidemic encephalitis 14 years prior to the air studies and whose admission diagnosis was post encephalitic behavior disorder. Pneumoencephalography demonstrated the two lateral ventricles to be confluent medially. The vertical midline shadow normally produced by the septum pellucidum was absent. Otherwise, the ventricles appeared to be in their normal position and of normal size. The authors concluded that the disappearance of the septum pellucidum most likely occurred during fetal development.

Berkwitz and Rigler[4] reported a case of tuberous sclerosis in which the diagnosis was established by pneumoencephalography and absence of the septum pellucidum was incidentally demonstrated. The authors felt that there was not adequate hydrocephalus present to account for the absent septum pellucidum on that basis. Dolgopol[5] reported a case in which autopsy demonstrated absence of the septum pellucidum as the only anomaly present in the brain. The patient was a 60 year old woman who had a normal neurologic examination at the time of admission. Death occurred following occlusion of the axillary and femoral arteries. Autopsy disclosed absence of the septum pellucidum, in addition to moderate internal hydrocephalus. The corpus callosum was atrophic, as was the cerebral white matter. The ventricular dilatation was attributed to cerebral atrophy associated with the arteriosclerotic process. The etiologic factor responsible for the absence of the septum pellucidum was not established, however.

A case of congenital absence of the septum pellucidum associated with congenital amaurosis was described by Reeves.[6] The patient, a seven month old male infant, was observed to have a strabismus at five months. Blindness was also apparent. Funduscopic examination revealed bilateral optic atrophy; congenital aplasia of the optic nerves was suggested as the most probable cause. The strabismus and nystagmus were considered secondary to amaurosis. Pneumoencephalography demonstrated very convincingly the typical pattern of absence of the septum pellucidum. In the lateral view, the medial confluence of the anterior portions of the lateral ventricles and the normal separation posteriorly were cited as characteristic findings in this disorder. This case is of notable interest because of the occurrence of two congenital anomalies, seemingly unrelated.

Savain[7] presented the encephalographic findings of a case of congenital absence of the septum pellucidum. Again mention was made of the absence of the septum anteriorly with the normal separation of the lateral ventricles posteriorly. The patient was a 13 year old boy

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with the clinical diagnosis of migraine, in whom no abnormal findings were reported on physical examination.

Recently the authors had an opportunity to examine a patient in whom pneumoencephalography demonstrated the characteristic findings of absence of the septum pellucidum. The interest created by this case prompted this report.

CASE REPORT

An 18 year old girl entered the hospital with the complaint of convulsive seizures, three in number, occurring during the preceding five-month period. The first attack had appeared during sleep in the early morning hours. The parents were awakened by the patient's "choking noises;" when they arrived at the bedside she was unconscious and remained so for an estimated period of 15 minutes. Postictal confusion was present and she complained of severe generalized headache; she then slept for two hours. Some headache was present throughout the rest of the day. The second attack occurred four months later and again the time of onset was during the early morning hours. The parents stated that she had a fixed stare, all extremities became rigid, and clonic convulsive movements developed. Salivation was moderate. Incontinence or biting movements were not observed. The duration of the attack was estimated at five minutes. Upon regaining consciousness she complained of generalized headache. The patient recalled having a dream prior to the onset of this attack. During this dream she witnessed her own birth and early babyhood years. Later on during the dream she died. After this stage she remembered "things going around and around" and with that her mental processes terminated. The third attack took place on the following day and was identical with the second in all respects. This attack, too, was preceded by a dream during which she was on top of a high mountain. She was about to fall from the mountain-top when the dream ended.

Following each of the three attacks the patient complained of weakness in both lower extremities. This weakness persisted throughout the course of the day and her gait was described as drunken. These difficulties always subsided completely within 12 hours after an attack.

The patient was the youngest of four siblings. The oldest sibling had asthma. Otherwise the health of these family members was excellent. The patient's mother had had convulsive seizures when stricken with pertussis at the age of two years. She had had no further attacks after this illness. The father's health was excellent. The patient's birth and early development were normal. She had had the usual childhood diseases without known complications. She had just recently graduated from high school and had successfully made arrangements for employment as an office worker in the home locality.

Physical examination revealed a young girl of healthy appearance and slight stature who was alert and cooperated well. She was properly oriented in all spheres. The blood pressure was 100/60 mm. Hg. Visual acuity was 10/100 in the right eye and 10/200 in the left eye. With correction, the visual acuity was normal. The pupils measured 5 and 6 millimeters, respectively, and reacted sluggishly to light. The optic disk margins were blurred but no true elevation existed. The visual fields as determined by the tangent screen method were normal. The blind spots were of normal size. The remainder of the examination was entirely normal. There was no evidence of neurologic deficit.

Laboratory findings. Routine studies of the blood and urine were normal. The photofluorogram of the chest was normal. Roentgenograms of the skull revealed a triangular area of calcification in the midline in the occipital area. This radiopaque area was presumably in the falx cerebri at the point of juncture of the latter with the tentorium cerebelli anteriorly. The electroencephalogram revealed unusually fast (28-32/second) wave activity of low voltage (5-15 microvolts) in the occipital areas. No spike activity, focal slow, or amplitude asymmetries were noted. Spinal fluid examination produced clear colorless fluid under an initial pressure of 90 mm. There were three white cells per cu.mm. and the Pandy test revealed a trace of globulin. The total protein was 37 mg. per cent. Serologic tests for syphilis carried out both on the blood and spinal fluid were negative. The fasting blood sugar was 57 mg. per cent.

Pneumoencephalography was carried out eight days after the initial admission; 110 cc. of spinal fluid was removed and replaced with an equivalent amount of air in 10 cc. increments. The patient tolerated the procedure satisfactorily. This examination revealed an absence of the normal partition of the lateral ventricles with a confluence of the air mass in the midline anteriorly (figures 1, 2, and 3). No other abnormalities were noted. The defect becomes more striking when compared with the normal pneumoencephalogram.

The patient recovered promptly from the effects of the air test. She was placed on anticonvulsant medication and discharged from the hospital two days later.

DISCUSSION

Absence of the septum pellucidum cannot be determined clinically. Prior to 1935 all cases of this anomally were identified only at autopsy or during routine anatomical dissection. Dyke and Davidoff[3] were able to demonstrate the disorder by means of pneumoencephalography, and other similar cases have since been recorded in the literature. As Hoch-

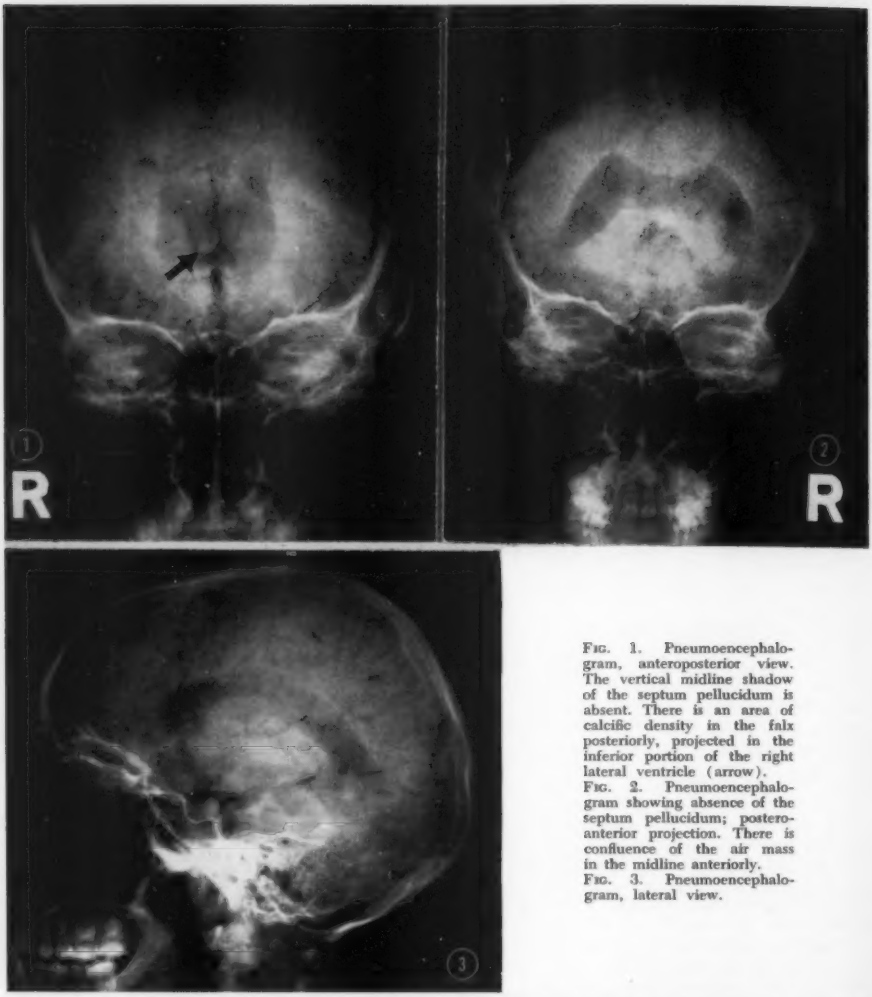

FIG. 1. Pneumoencephalogram, anteroposterior view. The vertical midline shadow of the septum pellucidum is absent. There is an area of calcific density in the falx posteriorly, projected in the inferior portion of the right lateral ventricle (arrow).
FIG. 2. Pneumoencephalogram showing absence of the septum pellucidum; posteroanterior projection. There is confluence of the air mass in the midline anteriorly.
FIG. 3. Pneumoencephalogram, lateral view.

stetter[2] emphasized in his report on the subject, the occurrence of this anomaly as an isolated abnormality is exceedingly rare. Absence of the septum pellucidum is an expected finding in congenital absence of the corpus callosum. Tumors of the diencephalic region not uncommonly lead to the production of rents or defects in the septum pellucidum. This presumably is a mechanical process due to the increased pressure resulting from the obstructive hydrocephalus.

There is no simple explanation for complete absence of the septum pellucidum in an otherwise normal brain. Previous authors including Reeves[6] and Dolgopol[5] have presented Hochstetter's thesis that the septum pellucidum is formed along with the corpus callosum and the hippocampal commissure during the early prenatal months. Hochstetter suggested that a cavity appears between the dorsal leaves of the septum pellucidum, which then is obliterated by a normal process of resorption. Were this

process of resorption to continue unabated beyond normal limits, the result would be absence of the septum pellucidum in the presence of a normal corpus callosum.

The origin of these midline structures appears to follow a thickening of the dorsal margins of the lamina terminalis. From this point the corpus callosum develops caudally and, during this process of retrograde growth, draws backward on its under surface a sheet of tissue arising from a membranous portion of the lamina terminalis. This is the origin of the septum pellucidum which eventually separates the true lateral ventricles and connects the corpus callosum with the fornix. According to Strong and Elwyn,[8] the anlage of the septum pellucidum is that area of the lamina terminalis not occupied by commissural fibers. It is conceivable that during the early stages of fetal development all portions of the lamina terminalis are given to these commissural fibers and no areas remain for development of the eventual septum. This, then, would constitute true agenesis or aplasia of the septum pellucidum in the presence of other normal midline structures.

SUMMARY

Congenital absence of the septum pellucidum as an isolated finding by pneumoencephalography has been described. The patient sought help for convulsive seizures, but showed no evidence of neurologic deficit. Other abnormalities capable of acting as epileptogenic foci may exist. It is doubtful if the absent septum pellucidum is directly related to the seizure phenomena. Reports in the literature dealing with this anomaly have been reviewed and the embryologic processes leading to its development discussed.

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2. Hochstetter, F.: Ueber Fälle vom vollständigen Fehlen des Septum pellucidum beim Menschen. Sitzber. Akad. Wiss. Wien 132-133:1, 1925.
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■ Dr. Abercrombie admits of apoplexy from interrupted circulation; and "thinks that this principle will be found to accord with all the phenomena of simple apoplexy." The causes of this interrupted circulation, he observes, may be referred to the following heads:—"Derangement of the relation betwixt the arteries and veins of the brain in connection with a general state of plethora; causes which directly diminish the capacity of the venous system of the brain, or any part of it; diseases of the sinuses impeding the passage of the blood from the veins, or diminishing the area of the sinuses at particular parts; interruption of the circulation in the veins of the neck; and disease of the lungs and of the heart. Dr. Abercrombie adds, the circulation of the brain may be interrupted by diminution of the impulse of blood entering the head as in syncope, and disorders of extreme exhaustion."

John Cooke in *A Treatise on Nervous Diseases,* published in 1824.

CASE REPORT

Akinetic mutism

David D. Daly, M.D. and J. Grafton Love, M.D.

In 1941 Cairns and co-workers[1] proposed the term "akinetic mutism" to characterize a curious clinical state which they described as follows:

The patient sleeps more than normally, but he is easily roused. In the fully developed state he makes no sound and lies inert, except that his eyes regard the observer steadily, or follow the movements of objects, and they may be diverted by sound. Despite his steady gaze, which seems to give promise of speech, the patient is quite mute, or he answers only in whispered monosyllables. Oft-repeated commands may be carried out in a feeble, slow, and incomplete manner, but usually there are no movements of a voluntary character; no restless movements, struggling, or evidence of negativism. Emotional movement also is almost in abeyance. A painful stimulus produces reflex withdrawal of the limb, and, if the stimulus is sustained, slow feeble voluntary movements of the limb may occur in an attempt to remove the source of stimulation, but usually without tears, noise, or other manifestations of pain or displeasure. The patient swallows readily, but has to be fed. Food seen may be recognized as such, but there is evidently little appreciation of its taste and other characteristics; objects normally chewed or sucked may be swallowed whole. There is total incontinence of urine and feces.

In this original report the syndrome appeared in a patient with a cyst of Rathke's pouch invading the third ventricle. Aspiration of the cyst relieved the symptoms.

Subsequently Cairns[2] remarked that he had observed akinetic mutism in other lesions near the third ventricle or following ventriculography or operation in cases of severe obstructive hydrocephalus incident to stricture of the aqueduct of Sylvius. He commented that mutism without akinesia also occurred.

Recently we have observed this syndrome in a patient with a lesion in the region of the mesencephalon. Because of the paucity of recorded instances of this syndrome, it seemed worthwhile to report it.

REPORT OF CASE

A 14 year old boy from Chile was registered at the Mayo Clinic on July 26, 1957. The following history was obtained from the parents and the patient by a Spanish-speaking physician. In the early hours of June 19 the patient was awakened by a severe bursting headache which lasted about 15 minutes; afterward he was drowsy and slept again for about three hours. On July 7 he experienced a sudden severe pain at the base of the skull; this persisted for less than a minute. On July 10 he was again awakened by a severe bursting headache. Examination two days later revealed papilledema.

Physical examination disclosed no significant finding. The patient appeared to be an alert, pleasant youth of normal intelligence. Neurologic examination was normal, except for bilateral papilledema of 2 diopters. Results of routine laboratory tests were within normal limits, except for roentgenograms of the skull which showed increased digital markings.

On August 2 ventriculography was performed. This disclosed marked dilatation of the lateral and third ventricles due to high-grade obstruction at the cephalic end of the aqueduct. With the patient in the upright position in the Adson chair, bilateral suboccipital craniectomy was performed through a midline incision. Splitting the vermis revealed a gray granular tumor filling the upper portion of the fourth ventricle. The tumor was removed piecemeal; however, at the end of the dissection a small amount of tumor remained around the circumference of the inferior end of the dilated aqueduct. It was felt that this could not be removed because of its firm attachment to the midbrain. Histologic examination of the tumor revealed an astrocytoma, grade 1.

In the early evening following operation the patient was in deep coma, with elevated blood pressure, pulse rate of 136 beats per minute, and respirations of 30 per minute. Later that evening there was some lightening of the coma, and the patient began to move his extremities. The next day the patient slept almost continuously but

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could be aroused by being spoken to. On command he would grasp his father's hand. Although he lay inert, infrequent movements of all extremities suggested that no paralysis existed. He responded to aspiration by coughing and gagging, but he did not speak or utter any sounds. He did not move his eyes and the right eye stayed in the divergent position. The pupil of the right eye was larger than the left and did not react to light. By the third postoperative day the patient moved all extremities without signs of weakness. He would grasp objects firmly with both hands and protrude his tongue on request, but he remained mute. When food was placed in his mouth, he would not chew it; nevertheless he readily swallowed liquids put into his mouth. He was incontinent of feces. When undisturbed he was somnolent and inactive. When stimulated he seemingly was aware of, but indifferent to, his environment. Spontaneous movements were few, and he would maintain apparently uncomfortable postures without evident distress. Occasionally he tugged feebly at the nasal and urinary catheters. Noxious stimuli, such as venipuncture, were disregarded.

In the succeeding days a slow but constant improvement occurred. One week after operation the patient appeared aware of his environment and cooperated slowly with the requests of his Spanish-speaking nurse. Yet he continued mute. Noxious stimuli evoked only half-hearted, ineffectual movements of withdrawal and spontaneous activity was limited. Although he seemingly recognized his parents, he showed no emotional response to them. His features were expressionless, and he had no interest in the activities about him. When left undisturbed he slept much of the time. At the end of two weeks he had yet to utter a sound. Dysphagia, which had been present initially, had virtually disappeared and he could chew and easily swallow food placed in his mouth. He obeyed simple commands and communicated with his parents by sign language. He would point to his mouth when he was hungry and to his penis when he desired to urinate. Spontaneous movements were sparse and he still appeared apathetic and indifferent, although to a lesser degree than during the previous week. The right eyelid was ptosed and the globe remained in the divergent position. The left eye was held below the horizontal plane and it had a constant downward nystagmus. Extension of his arms evoked a coarse tremor which increased in the terminal phases of movement. He still slept excessively, although he could be roused readily. He moved more frequently than before and would move his limbs to avoid an awkard position. Because of his slow progress, we decided during the third postoperative week to attempt stimulation with analeptic drugs. He was given 40 mg. of methylphenidate hydrochloride intravenously; this produced marked increase in alertness and responsiveness. He was able to carry out more complex requests than before; for example, by holding up his fingers he could indicate the number of persons in the room or could point to his parents on request. He thenceforth received the drug by mouth in a total daily dose of 100 mg. in divided doses of 20 mg. each. This sharply accelerated the rate of improvement; he slept less, showed more spontaneous movements, and attempted to walk with help. However, he remained mute.

One month after operation the patient was able to follow moderately complicated commands such as, "touch your right index finger to your left ear." When given several different commands successively, he had increasing difficulty and began to perseverate. Attempts at more accurate testing were difficult to evaluate, since it was not clear whether his failures resulted from lack of comprehension or apathy and indifference. In any event, on doing portions of the Stanford-Binet, Wechsler-Bellevue, and progressive matrices tests, the patient was unable to perform beyond the six-year level. He was able to read a simple written command and execute it properly. He could purse his lips, but would not whistle. He coughed vigorously and swallowed without trouble; yet he had still made no effort to speak. He usually lay quietly in bed, watching the activities around him. He showed no emotion, even with his parents. At his mother's request he would place his arms about her and kiss her; however, the action was a stiff mechanical gesture which suggested the behavior of a puppet. Muscle strength was normal, although he had a coarse tremor of the head at rest and movement evoked a similar coarse tremor of arms and legs. There was paralysis of function of the third and fourth cranial nerves on the right side and of the fourth and sixth nerves on the left. Conjugate movements of the eyes also seemed defective. Sensation, which by now could be tested reliably by sign language, seemed intact in all modalities.

On September 5 the patient spoke for the first time when he called his parents by name. Later that day he mentioned his sister's name, and when his father told him he was to be taken to a neurologic conference, he asked: "Why?" Two days later he said, "Good morning, Doctor." The content of his speech rapidly increased in complexity during the next few days. Within one week he spoke lucidly, but with a scanning measured speech of cerebellar type. He became more interested in his environment and wanted to read magazines. He expressed interest in going home and told his parents that he wished to visit Chicago on the way.

In the following two weeks the content of his speech and his affective behavior returned to normal. Although he was still troubled by his ocular palsies and ataxia, he worked vigorously at rehabilitation in the department of physical medicine. His normal affective response returned, and he would laugh appropriately at jokes and would in turn make jokes. He exhibited considerable interest in learning English and made rapid prog-

ress so that it was soon possible to speak to him in simple sentences. His parents felt that his vocabulary and syntax in Spanish had returned to its preoperative level. At the time of dismissal on September 27 he had mild cerebellar speech and moderate ataxia. The ocular palsies persisted but were improving.

When questioned as to what he recalled of his illness, he said that he remembered his arrival at the clinic but not his admission to the hospital nor any of the events of the day of his operation. Postoperatively, he was amnesic until the third day after he had begun to speak. He was unable, therefore, to contribute anything to our understanding of the reasons for his mutism. At the time of his dismissal he was still taking methylphenidate hydrochloride, 60 mg. daily. On several occasions attempts were made to discontinue its use. Whenever it was stopped for a period of a day, the patient became apathetic and somewhat somnolent. On resuming its use, he would return to a state of normal alertness.

COMMENT

Cairns[2] observed that lesions of the upper part of the brainstem usually result in continuous unconsciousness that resembles normal sleep, with quiet respiration, muscular relaxation, and loss of the expression of wakefulness. He termed this state "hypersomnia" and regarded akinetic mutism as a variant of it. Similar conclusions have been expressed by Geoffrey Jefferson and Johnson[3] who coined the word "parasomnia" to refer to "a trance-like state of stupor which closely resembles normal sleep." However, although commenting that patients passed through a phase of drowsiness, they did not report any instances of mutism.

The literature contains numerous descriptions of hypersomnia or parasomnia and some of the patients described have been mute; however, in many of them mutism occurred in a setting of rather marked clouding of consciousness. In discussing a midbrain syndrome following head injury, Kremer, Russell, and Smyth[4] made passing reference to mutism in four patients. They regarded the mutism as due to an inability to "coordinate breath expulsion with glottis closure and articulation." Such an explanation does not seem to apply to our patient who was able to cough effectively and swallow normally while still mute.

Other instances of altered consciousness in patients with presumed lesions of the brainstem were reported by Michael Jefferson.[5] Most of his patients experienced profound depression of consciousness although one patient (case 1) presented a picture somewhat suggestive of akinetic mutism.

Bailey[6] described what he regarded as akinetic mutism in a patient with anoxic degeneration of the neocortex; however, the behavior which he described does not conform to the criteria laid down by Cairns and co-workers.[1] Bailey's patient lay in extensor rigidity with her eyeballs moving aimlessly; she gave no signs of recognition of any person in her environment. Necropsy revealed severe degeneration of the entire neocortex, with preservation of the nuclear masses of the bulb, pons, midbrain, and hypothalamus. Cairns[2] previously had given consideration to the degree of "consciousness" that might exist in human anencephalic and hydrocephalic monsters. He concluded that they exhibited "at best a vague rudimentary awareness, chiefly through the special senses and viscera, with limited range and crude quality of analysis. . . . He seemed reluctant to apply the appellation "consciousness" to this state. Thus, we conclude that Cairns distinguished hypersomnia and akinetic mutism from the dim and flickering perceptions of decorticated human beings.

Mason-Browne[7] described a case in which akinetic mutism followed an operation for a craniopharyngioma that extended into the region of the third ventricle and hypothalamus. This patient suffered great deterioration of her capabilities, being, for example, unable even to attempt to sign her name. Seemingly she spoke not at all and reacted little to her environment. This state persisted for about ten days, following which some improvement occurred. However, she made only a slight recovery and died six months after operation.

Studies of animals with experimentally produced lesions in the same region have demonstrated analogous alterations in behavior. Ingram, Barris, and Ranson[8] described a condition in cats which they termed "catalepsy." They observed that "lesions involving the caudal part of the hypothalamus and the upper part of the mesencephalic tegmentum may produce a syndrome characterized by initial somnolence, persistent loss of motor initiative, marked disinclination to walk, acceptance of passively induced poses, indisposition to eat

even when hungry, and vacuity of expression. . . . There was strong suppression of emotional reactions in many cases." Later Bailey and Davis[9] placed lesions in the periaqueductal region of cats and produced a state which they specifically compared to akinetic mutism. They found that "if the lesion is extensive, the cat lies inert, silent, and flaccid as a wet rag." Later, if stimulated, the cat might walk about slowly, but it would show no spontaneous movements and would not eat. The acute stage which they described is similar to the results of acute injury to the reticular activating system which were described by Lindsley and co-workers.[10] By stimulation in the region of the "middle portion of the ventral nucleus of the thalamus," Hess[11] has been able to reduce or completely abolish motor activity, "adynamia," or to elicit states of sleep; conversely, stimulation in the caudodorsal portions of the hypothalamus and the central gray matter of the mesencephalon resulted in an increase in motor activity with impulses to take flight. These positive results of stimulation appear to be in accord with the negative effects of destructive lesions in the same area.

Of course, it also has been recognized that placidity, hypokinesia, and disregard of the environment may result from lesions located more rostrally in the hypothalamus and thalamus. The literature relating to this problem has been comprehensively reviewed by Bond and co-workers.[12] By their own studies these same authors have demonstrated that small bilateral lesions in the septum, fornix, and anterior thalamus produce behavioral alterations which included hypokinesia and "muscular plasticity," unresponsiveness to painful stimuli, indifference to food, and "impaired consciousness" manifested by poverty of reaction to environmental stimuli. They concluded that these abnormalities of behavior were not the consequence of damage to specific nuclear masses, but resulted from lesions "so situated as to interrupt major rhinencephalic–hypothalamic and mesencephalic reticulothalamocortical projections." These conclusions seem in agreement with the clinical observations of Cairns,[2] suggesting that akinetic mutism may result from a variety of lesions involving this general region.

The actions of our patient are consistent with the changes in behavior described in the experimental animals. Although there is no anatomic confirmation of the site of the lesion in our patient, the clinical findings permit us to infer its location. The ocular palsies, disturbances in conjugate movements of the eyes, and the ataxia and tremor, which imply disturbance of the dentatorubral-thalamic system, indicate involvement of the central portion of the mesencephalon. Furthermore, normal sensory perception suggests integrity of the lemniscal system. Finally, the presence of voluntary movements indicates preservation of the corticospinal motor tracts in the cerebral peduncles. Thus, we postulate a lesion in the mesencephalic tegmentum as the cause of the clinical picture observed.

If these assumptions are correct, we propose that the syndrome of akinetic mutism results from a partial defect in the reticular activating system. The term "akinetic mutism" is not entirely satisfactory since it unduly emphasizes mutism. Perhaps the syndrome should be interpreted in a broader sense as one in which hypokinesia and mutism are facets of a more general defect–unresponsiveness to, or withdrawal from, environmental stimuli. Concomitant with this are apathy and loss of appropriate affective responses, not only to noxious stimuli but to pleasurable ones as well. Somnolence is still another consequence of reduction in the normal activity of the reticular system. Thus, dampening of the normal tonic action of the reticular-activating system results in an over-all decline in alertness and responsiveness. Unfortunately, we shall never know if this is really the subjective experience of these patients since they are all amnesic for their experience.

SUMMARY

From the case of akinetic mutism with a midbrain lesion described, and a review of the literature and experimental observations bearing on this problem, we conclude that the syndrome results from an incomplete defect in the functioning of the reticular activating system.

ADDENDUM

After this paper was submitted, the case of Riser and associates[13] has come to our attention. These authors described akinetic mutism

developing in a patient with localized hemorrhage of the mesodiencephalon. Necropsy revealed an angiomatous malformation in this region.

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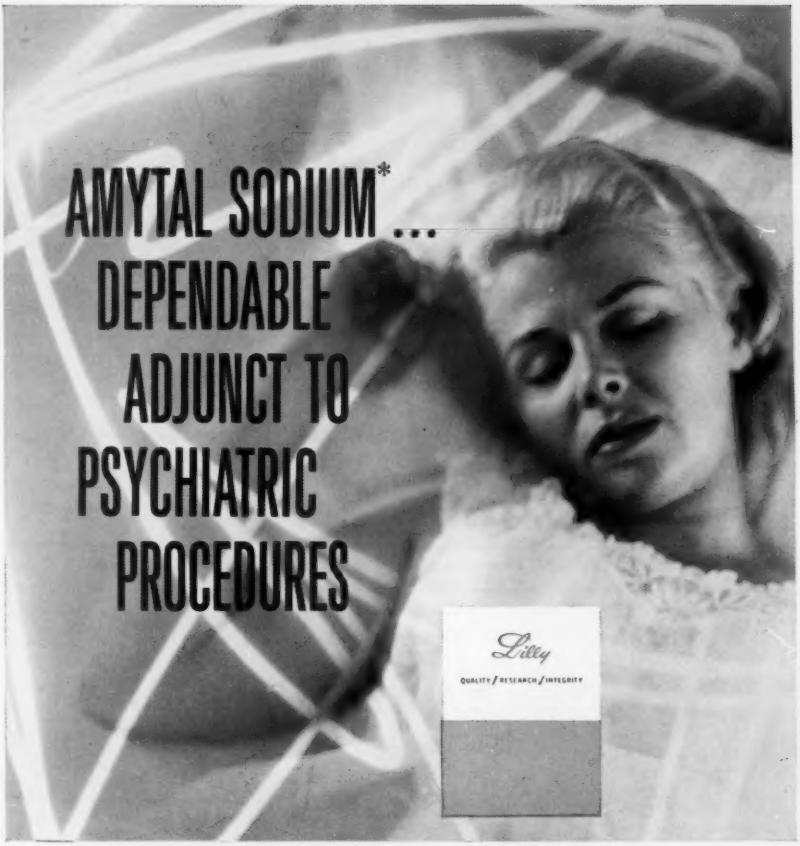
■ It is not enough to say that speech consists of words. It consists of words referring to one another in a particular manner; and without a proper interrelation of its parts a verbal utterance would be a mere succession of names embodying no proposition. A proposition—*e.g.* gold is yellow—consists of two names, each of which, by conventional contrivances of position, etc. (called grammatical structure in well-developed languages), modifies the meaning of the other. All the names in a random succession of words may, it is true, one after the other, excite perceptions in us, but not perceptions in any relation to one another deserving the name of thought. The several perceptions so revived do not make a unit. We are *told* nothing by a mere sequence of names, although our organisation is stirred up by each of them. Now, a proposition is not—that is to say, in its effect on us is not—a *mere* sequence.

When we apprehend a proposition, a *relation between two things* is given to us—is for the moment, indeed, forced upon us by the conventional tricks which put the two names in the respective relations of subject and predicate. We receive in a *two-fold* manner, not the words only, but the order of the words also.

J. Hughlings Jackson in *Notes on the Physiology and Pathology of the Nervous System*, published in 1868.



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NEWSLETTER

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MARCH 1958

Albany Expands Neurology Albany Medical College has made a "significant expansion" in its department of neurology aimed at developing clinical teachers and promoting research in neurologic science, according to Dr. Harold C. Wiggers, dean of the school. Foremost in this expansion is the activation of a well equipped neuropathology laboratory. This laboratory, which operates in conjunction with the pathology departments of the medical school, Albany Hospital, and the local Veterans Administration Hospital, will make possible the training of graduate students in resident positions in neuropathology.... Three faculty changes have been made in the new program. Frederick H. Hesser is now professor of neurology and chairman of the department, succeeding Robert W. Graves who resigned last summer. Dr. Lewis D. Stevenson and Dr. David W. Sinton have joined the neurology teaching staff, Dr. Stevenson as a lecturer in neurology and neuropathology, and Dr. Sinton as assistant professor of neurology and instructor in neuropathology. Drs. Hesser and Sinton are, respectively, neurologist-in-chief and clinical assistant in neurology at Albany Hospital. Dr. Stevenson was formerly professor of clinical neurology at Cornell University Medical College and was also an associate professor of neuropathology at both Cornell and New York University. He served as consulting neurologist at New York and French Hospitals, and is a graduate of Queen's University, Canada. Dr. Sinton previously was instructor in neurology at the University of Iowa and the University of Colorado.

American Board to Hold Two Examinations in 1958 The American Board of Psychiatry and Neurology will hold two examinations in 1958. The first will be conducted in San Francisco (March 17-18) and the second in New York City (Dec. 15-16).... The board also announces that training credit for fulltime neurologic and/or psychiatric assignment in unapproved military programs or services during the Korean emergency (Jan. 1, 1950 to Jan. 1, 1954) will be terminated as of Jan. 1, 1959.... All communications on matters pertaining to the board should be addressed to David A. Boyd, Jr., Secretary-Treasurer, American Board of Psychiatry and Neurology, Inc., 102-110 Second Avenue, S. W., Rochester, Minnesota.

Thompson Becomes President of the Neurological Surgeons At the seventh annual meeting of the Congress of Neurological Surgeons at the Hotel Statler in Washington, D. C. (Nov. 7-9, 1957), Raymond K. Thompson was elected president, succeed-

ing Frederick C. Rehfeldt; Philip D. Gordy, vice-president; and Richard L. DeSaussure, secretary-treasurer. Executive committee members are Edward C. Weiford, John R. Russell, and Robert Weyand.... During the Washington meeting, Dr. Francis C. Grant was the honored guest speaker. Also, a postgraduate seminar was held at the Armed Forces Institute of Pathology and the National Institute of Neurological Diseases and Blindness in Bethesda on Nov. 6.

Neurological Foundation Emphasizes Basic Research A voluntary group, the National Neurological Research Foundation, has been organized in Washington, D. C. The purpose of the foundation is to foster "across-the-board" basic research in the nervous system in order to enrich the substratum of our knowledge of structures and mechanisms underlying chronic neurologic disorders. The foundation does not oppose "target" research in categorical disease areas, but believes that serendipity should be encouraged and that more emphasis should be placed on "free-wheeling" basic research to broaden the base of our knowledge of the nervous system. This has become the foundation's mission, which it hopes to achieve through the award of five-year fellowships to physicians and scientists who, standing on their merit, wish to pursue their investigations free from restrictions of protocol. The fellowships provide a stipend of $10,000 to $12,000 a year for a period of five years.... Chairman of the officers and trustees of the foundation is Dr. Fuller Albright, distinguished endocrinologist at Harvard. Raymond D. Adams heads the scientific advisory committee, which includes Edward M. Dempsey, Louis S. Goodman, Seymour S. Kety, Oliver Lowry, H. W. Magoun, James L. O'Leary, and A. Earl Walker. Inspiration for the creation of the foundation came from its executive secretary, Mrs. Rodgers Denckla, who directs the foundation's national headquarters at 3255 N Street, N. W., Washington 7, D. C.

NCRND Meets in New York Under the chairmanship of A. B. Baker, the National Committee for Reseach in Neurological Disorders (Newsletter, July 1954) held its annual meeting in the New York Athletic Club, New York City (Dec. 12, 1957). Present at the meeting were representatives from the Association for the Aid of Crippled Children, National Epilepsy League, National Association for Retarded Children, United Cerebral Palsy Association, National Multiple Sclerosis Society, Muscular Dystrophy Associations of America, National Society for Crippled Children and Adults, American Foundation for the Blind, National Society for the Prevention of Blindness, and the New York Association for the Blind. Representatives from the following organizations were unable to attend: National Foundation for Eye Research, National Council to Combat Blindness, and the National Foundation for Infantile Paralysis. The major portion of the meeting was devoted to a review of the year's activity at the National Institute of Neurological Diseases and Blindness by Dr. Pearce

Bailey, director of NINDB, and by the assistant director, Dr. Richard L. Masland.

Basal Ganglia Surgery to be Subject for Three-Day Symposium Under the sponsorship of New York University and the American Rehabilitation Foundation, there will be a three-day symposium (May 15-17) on "Surgery of the Basal Ganglia for Extrapyramidal Diseases." The purpose of this symposium is to conduct a critical inquiry into the present status of this type of surgery and into some of the clinical and physiologic aspects of the basal ganglia. The symposium will take place in the new alumni hall of New York University College of Medicine at 550 First Avenue in New York City.... Included in the program is a symposium on neuroanatomic and physiologic aspects of basal ganglia surgery, moderated by Raymond S. Snider; a panel discussion conducted by A. Earl Walker on present surgical technics; and a clinical demonstration of long-term postoperative patients to be presented by Robert S. Schwab. Other panel members and speakers are Henry T. Wycis, Adolph Spiegel, T. Riechert, Nicholas Wetzel, Luis Amador, Percival Bailey, Gonzalo Bravo, M. Riklin, William Sweet, Russell Meyers, D. Denny-Brown, S. Bernard Wortis, and Irving S. Cooper.

Bairati in the U. S. as a Visiting Scientist Professor Angelo Bairati, pioneer authority on the fine structure of the nervous system and professor of anatomy and director of the institute of human anatomy at the University of Milan, is again in this country as a visiting scientist. Professor Bairati will be associated with Sanford L. Palay, head of the section on neurocytology, in William F. Windle's laboratory of neuroanatomic sciences at the National Institute of Neurological Diseases and Blindness. These two scientists will collaborate on problems in electronmicroscopy. Professor Bairati will not be a stranger in Bethesda, for he participated in the conference on the biology of the neuroglia held at NINDB two years ago, and two members of the NINDB staff are his former pupils, M. Fuortes and Cosimo Ajmone-Marsan.... Professor Bairati is on the faculty which will present the special review course on Fine Structure of the Nervous System to be given at the annual meeting of the American Academy of Neurology at the Bellevue-Stratford Hotel in Philadelphia (April 21-26, 1958).

New Directory of AAN Membership to be Ready Soon Mrs. J. C. McKinley, executive secretary of the academy, announces that the new directory of AAN members will be ready for distribution at an early date. The current roster of AAN members shows a total membership of 1,783. The present tally of members shows 9 honorary, 51 honorary-corresponding, 746 fellows and actives, 295 juniors, and 679 associates, the majority coming from 47 states, Puerto Rico, and Canada, with a lesser number from Central America, South America, Europe, Asia, and the Orient....

The six leading states in current AAN membership are New York (350), California (143), Massachusetts (109), Pennsylvania (104), Maryland (85), and Illinois (78).... Inquiries on AAN membership should be sent to Dr. Pearce Bailey, Chairman, AAN Membership Committee, National Institute of Neurological Diseases and Blindness, Bethesda 14, Maryland.

Foundation Established for Tay-Sachs' Disease

A new nonprofit foundation, the National Tay-Sachs' Association, Inc., New York Chapter, has been established to stimulate and support research and care programs in the heredofamilial, neurodegenerative diseases of infancy and childhood. The program is especially directed to Tay-Sachs' disease, Niemann-Pick's disease, infantile Gaucher's disease, Schilder's disease, diffuse sclerosis, amyotonia congenita, Friedreich's ataxia, and allied conditions. The foundation is cooperating with a current research program in these conditions at the Jewish Chronic Disease Hospital in Brooklyn, New York. This hospital now conducts a special clinic for outpatient care of afflicted children, and is constructing a special ward for the care and observation of inpatients. Both of these programs are coordinated with the laboratory research activities of the Isaac Albert Research Institute of the hospital. In addition, a comprehensive genetic study of these disorders is being made from histories supplied by the foundation and parents who have children under the care of the hospital. To develop further its genetic studies, physicians in hospitals throughout the country are being requested to inform parents of children afflicted with these conditions of the existence of the foundation.... For further information, communications should be addressed to the Medical Committee, National Tay-Sachs' Association, Inc., New York Chapter, P. O. Box 1250, G.P.O., New York 1, New York.

Cerebral Palsy Academy Elects New Officers

The American Academy for Cerebral Palsy at its 11th annual meeting in the Roosevelt Hotel, New Orleans (Nov. 24-27, 1957) elected William T. Green, president; Robert A. Knight, president-elect; and Samuel B. Thompson, treasurer. Raymond R. Rembolt continues as secretary and reappointed as chairman of the research committee was Chester A. Swinyard.... The 1958 annual meeting of the AACP will be at the Sheraton Biltmore Hotel, Providence, Rhode Island (Sept. 25-27).

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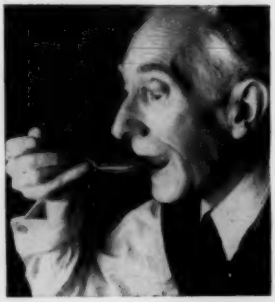

Above and right are action pictures, taken from a Warner-Chilcott film study, of a parkinsonian patient before and after initiation of Parsidol therapy for major tremor.

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*REFERENCE: Tucker, K. and Wilensky, H.: A clinical evaluation of meprobamate therapy in a chronic schizophrenic population. Am. J. Psychiat. 113:698, Feb. 1957.

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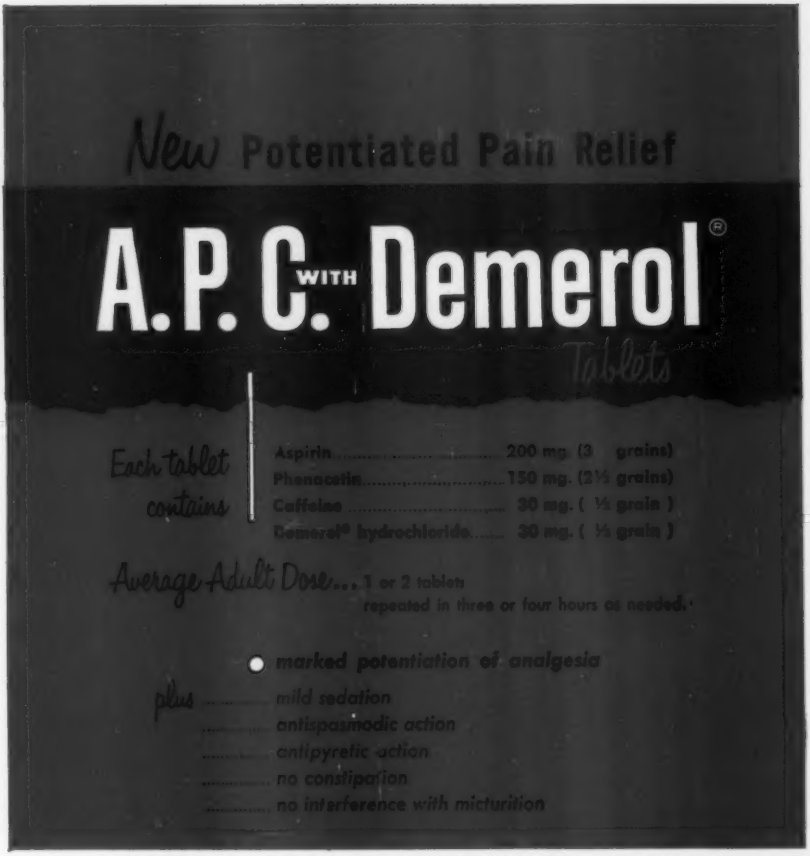
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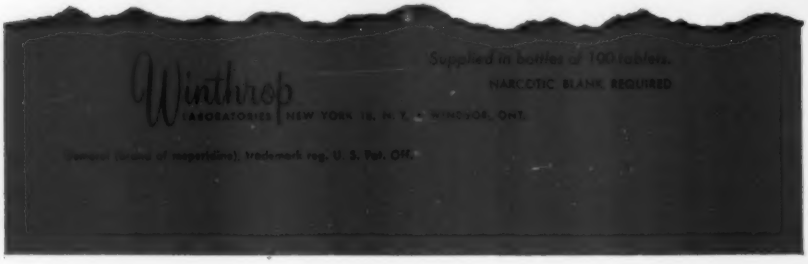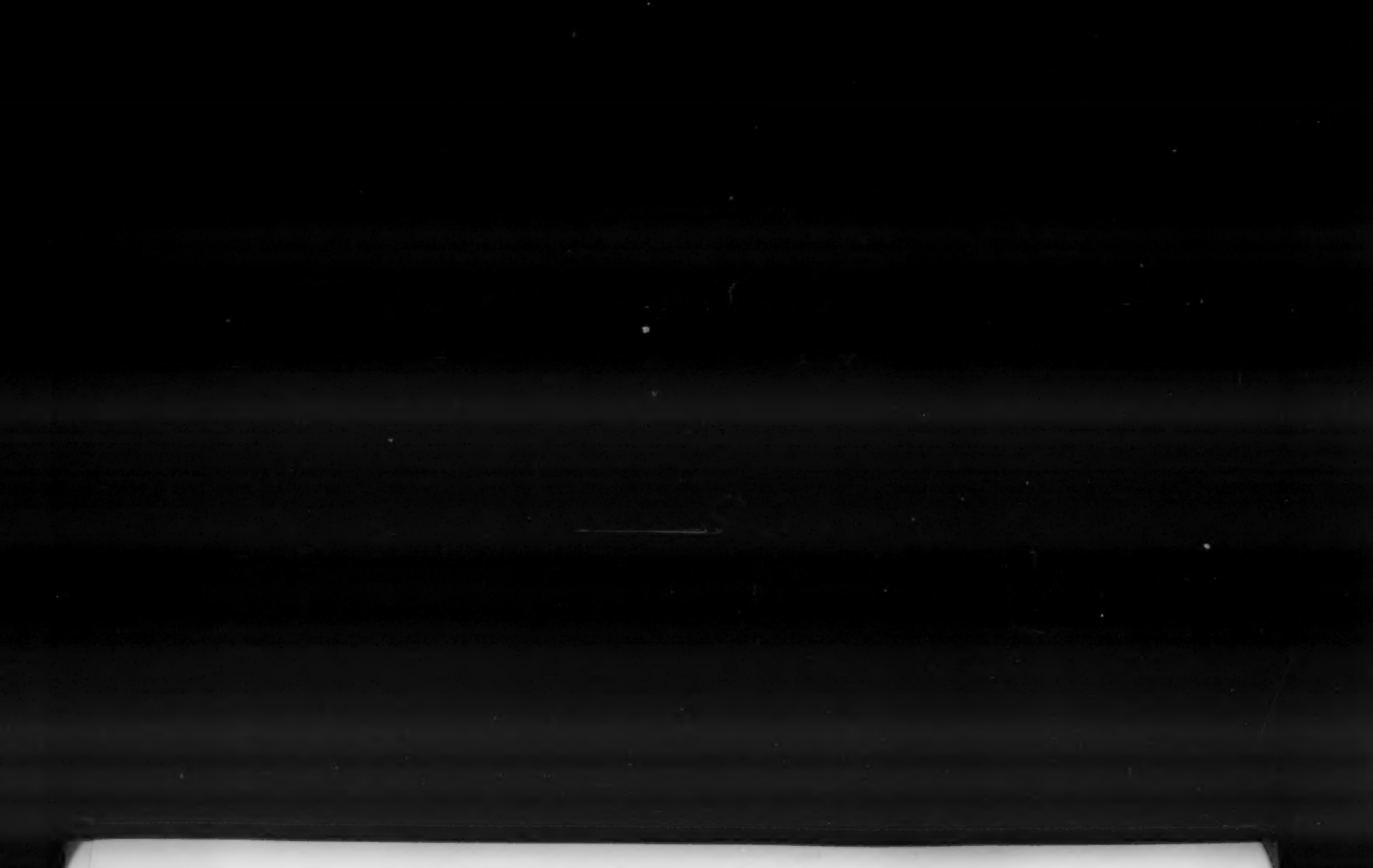
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